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Guidance for Industry

Stability Testing of Drug Substances and Drug Products

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**U.S. Department of Health and Human Services
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Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
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GUIDANCE FOR INDUSTRY¹

Stability Testing of Drug Substances and Drug Products

*(Due to the length and complexity of this draft document,
please identify specific comments by line number.)*

1 I. INTRODUCTION

2 The guidance is intended to be a comprehensive document that provides information on all
3 aspects of stability data generation and use. It references and incorporates substantial text from
4 the following International Conference on Harmonization (ICH) guidance:

- 5 • *ICH Harmonized Tripartite Guideline for Stability Testing of New Drug Substances and*
6 *Products, September 23, 1994 [ICH Q1A]*
- 7 • *ICH Guideline for Stability Testing of New Dosage Forms [ICH Q1C]*
- 8 • *ICH Guideline for Photostability Testing of New Drug Substances and Products [ICH Q1B]*
- 9 • *ICH Guideline for Stability Testing of Biotechnological/Biological Products [ICH Q5C].*

10 Where text from one of these documents has been incorporated in this guidance, it has been
11 denoted by the use of a reference in square brackets in the beginning of a particular section or at
12 the end of an individual paragraph.

13 The purpose of stability testing is to provide evidence on how the quality of a drug substance or
14 drug product varies with time under the influence of a variety of environmental factors such as
15 temperature, humidity, and light. Stability testing permits the establishment of recommended
16 storage conditions, retest periods, and shelf lives. [ICH Q1A]

17 This guidance provides recommendations regarding the design, conduct and use of stability
18 studies that should be performed to support:

- 19 • Investigational new drug applications (INDs) (21 CFR 312.23(a)(7)),

¹ This guidance has been prepared by the Stability Technical Committee of the Chemistry Manufacturing Controls Coordinating Committee (CMCCC) of the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration with input from the Center for Biologics Evaluation and Research (CBER). This guidance document represents the Agency's current thinking on stability testing of drug substances and products. It does not create or confer any rights for or on any person, and does not operate to bind FDA or the public. An alternative approach may be used if such an approach satisfies the requirements of the applicable statute, regulations, or both.

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- 20 • New drug applications (NDAs) for both new molecular entities (NMEs) and non-NMEs,
- 21 • New dosage forms (21 CFR 314.50(d)(1)),
- 22 • Abbreviated new drug applications (ANDAs) (21 CFR 314.92 - 314.99),
- 23 • Supplements and annual reports (21 CFR 314.70, and 601.12),
- 24 • Biologics license application (BLAs) and product license applications (PLAs) (21 CFR 601.2).

25 The principle established in ICH Q1A — that information on stability generated in any one of the
26 three areas of the EU, Japan, and the USA would be mutually acceptable in both of the other two
27 areas — is incorporated in this guidance document. In fact, much of the text of the guidance on
28 drug substances and drug products (Sections II.A. and II.B.) is incorporated directly from the
29 ICH Q1A text.

30 This guidance is intended to replace the *Guideline For Submitting Documentation for the*
31 *Stability of Human Drugs and Biologics*, published in February 1987. It applies to all drug
32 substances and products submitted to the Center for Drug Evaluation and Research (CDER).
33 This guidance also applies to biological products that are included in the scope of the ICH Q5C
34 *Stability Annex, Stability Testing of Biotechnology Drug Products* (July 1996) and all other
35 products submitted to the Center for Biologics Evaluation and Research (CBER).

36 The guidance provides recommendations for the design of stability studies for drug substances
37 and drug products that should result in a statistically acceptable level of confidence for the
38 established retest or expiration dating period for each type of application. The applicant is
39 responsible for confirming the originally established retest and expiration dating periods by
40 continual assessment of stability properties (21 CFR 211.166). Continuing confirmation of these
41 dating periods should be an important consideration in the applicant's stability program.

42 The choice of test conditions defined in this guidance is based on an analysis of the effects of
43 climatic conditions in the EU, Japan, and the USA. The mean kinetic temperature in any region
44 of the world can be derived from climatic data (Grimm, W., *Drugs Made in Germany*,
45 28:196-202, 1985, and 29:39-47, 1986). [ICH Q1A]

46 The recommendations in this guidance are effective upon publication of the final guidance and
47 should be followed in preparing new applications, resubmissions, and supplements. This guidance
48 represents FDA's current thinking on how the stability section of drug and biologics applications
49 should be prepared. An applicant may choose to use alternative procedures. If an applicant
50 chooses to depart from the recommendations set forth in this guidance, the applicant is
51 encouraged to discuss the matter with FDA prior to initiating studies that may later be determined
52 to be unacceptable.

53 FDA recognizes that the time necessary for applicants to establish new procedures, install, and
54 commission the new temperature and relative humidity-controlled rooms/cabinets, carry out
55 appropriate stability studies on batches of product, and submit the information in an application
56 may prevent some applicants from generating data consistent with the recommendations in the
57 guidance for some time. However, since this guidance represents FDA's current thinking and
58 recommendations regarding stability, submission of data not conforming with this guidance is

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59 possible with justification. Applications withdrawn prior to publication of this guidance should
60 not normally have to include stability data in conformance with the guidance upon resubmission.
61 However, if new stability studies are conducted to support the submission, such studies should be
62 conducted as recommended in the guidance.

63 A comprehensive glossary has been included, which contains definitions of the major terms and
64 the origin of the definitions (e.g., ICH, CFR, USP) where applicable.

65 **II. STABILITY TESTING FOR NEW DRUG APPLICATIONS**

66 **A. Drug Substance**

67 Information on the stability of a drug substance under defined storage conditions is an integral
68 part of the systematic approach to stability evaluation. Stress testing helps to determine the
69 intrinsic stability characteristics of a molecule by establishing degradation pathways to identify the
70 likely degradation products and to validate the stability indicating power of the analytical
71 procedures used.

72 Stress testing is conducted to provide data on forced decomposition products and decomposition
73 mechanisms for the drug substance. The severe conditions that may be encountered during
74 distribution can be covered by stress testing of definitive batches of the drug substance. These
75 studies should establish the inherent stability characteristics of the molecule, such as the
76 degradation pathways, and lead to identification of degradation products and hence support the
77 suitability of the proposed analytical procedures. The detailed nature of the studies will depend on
78 the individual drug substance and type of drug product.

79 This testing is likely to be carried out on a single batch of a drug substance. Testing should
80 include the effects of temperatures in 10°C increments above the accelerated temperature test
81 condition (e.g., 50°C, 60°C) and humidity, where appropriate (e.g., 75 percent or greater). In
82 addition, oxidation and photolysis on the drug substance plus its susceptibility to hydrolysis across
83 a wide range of pH values when in solution or suspension should be evaluated. Results from
84 these studies will form an integral part of the information provided to regulatory authorities.
85 Light testing should be an integral part of stress testing. The standard test conditions for
86 photostability are discussed in the ICH Q1B guidance.

87 It is recognized that some degradation pathways can be complex and that under forced conditions,
88 decomposition products may be observed that are unlikely to be formed under accelerated or
89 long-term testing. This information may be useful in developing and validating suitable analytical
90 methods, but it may not always be necessary to examine specifically for all degradation products if
91 it has been demonstrated that in practice these are not formed.

92 Primary stability studies are intended to show that a drug substance will remain within
93 specifications during the retest period if stored under recommended storage conditions. [ICH
94 Q1A].

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95 1. Selection of Batches

96 Stability information from accelerated and long-term testing should be provided on at least three
97 batches. Long-term testing should cover a minimum of 12 months' duration on at least three
98 batches at the time of submission. The batches manufactured to a minimum of pilot plant scale
99 should be by the same synthetic route and use a method of manufacture and procedure that
100 simulates the final process to be used on a manufacturing scale. The overall quality of the batches
101 of drug substance placed on stability should be representative of both the quality of the material
102 used in preclinical and clinical studies and the quality of material to be made on a manufacturing
103 scale. Supporting information may be provided using stability data on batches of drug substance
104 made on a laboratory scale. [ICH Q1A]

105 The first three production batches² of drug substance manufactured post approval, if not
106 submitted in the original drug application, should be placed on long-term stability studies post
107 approval, using the same stability protocol as in the approved drug application. [ICH Q1A]

108 2. Test Procedures and Test Criteria

109
110 The testing should cover those features susceptible to change during storage and likely to
111 influence quality, safety and/or efficacy. Stability information should cover as necessary the
112 physical, chemical, biological, and microbiological test characteristics. Validated
113 stability-indicating test methods should be applied. The extent of replication will depend on the
114 results of validation studies. [ICH Q1A]

115 3. Specifications

116
117 Limits of acceptability should be derived from the quality profile of the material as used in the
118 preclinical and clinical batches. Specifications will need to include individual and total upper
119 limits for impurities and degradation products, the justification for which should be influenced by
120 the levels observed in material used in preclinical studies and clinical trials. [ICH Q1A]

121 4. Storage Conditions

122 The length of the studies and the storage conditions should be sufficient to cover storage,
123 shipment, and subsequent use. Application of the same storage conditions applied to the drug
124 product will facilitate comparative review and assessment. Other storage conditions are allowable
125 if justified. In particular, temperature-sensitive drug substances should be stored under an
126 alternative lower temperature condition, which will then become the designated long-term testing
127 storage temperature. The 6-month accelerated testing should then be carried out at a temperature
128 at least 15°C above this designated long-term storage temperature (together with the appropriate

² The terms *production batch* and *manufacturing scale production batch* are used interchangeably throughout this guidance to mean a batch of drug substance or drug product manufactured at the scale typically encountered in a facility intended for marketing production.

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129 relative humidity conditions for that temperature). The designated long-term testing conditions
130 will be reflected in the labeling and retest date. [ICH Q1A]

131 Where *significant change* occurs during 6 months of storage under conditions of accelerated
132 testing at $40^{\circ}\text{C} \pm 2^{\circ}\text{C}/75\% \text{RH} \pm 5\%$, additional testing at an intermediate condition (such as
133 $30^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \text{RH} \pm 5\%$) should be conducted for a drug substance to be used in the
134 manufacture of a dosage form tested for long-term at $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \text{RH} \pm 5\%$ and this
135 information should be included in the drug application.³ The initial drug application should
136 include at the intermediate storage condition a minimum of 6 months of data from a 12-month
137 study. [ICH Q1A]

138 *Significant change* at $40^{\circ}\text{C}/75\% \text{RH}$ or $30^{\circ}\text{C}/60\% \text{RH}$ is defined as failure to meet the
139 specifications.[ICH Q1A] If any parameter fails *significant change* criteria during the
140 accelerated stability study, testing of all parameters during the intermediate stability study should
141 be performed.

142 If stability samples have been put into the intermediate condition, but have not been tested, these
143 samples may be tested as soon as the accelerated study shows significant change in the drug
144 substance. Alternatively, the study at the intermediate condition would be started from the initial
145 time point.

146 Where a *significant change* occurs during 12 months of storage at $30^{\circ}\text{C}/60\% \text{RH}$, it may not be
147 appropriate to label the drug substance for controlled room temperature (CRT) storage with the
148 proposed retest period even if the stability data from the full long-term studies at $25^{\circ}\text{C}/60\% \text{RH}$
149 appear satisfactory. In such cases, alternate approaches, such as qualifying higher acceptance
150 criteria for a degradant, shorter retest period, refrigerator temperature storage, or more protective
151 container and/or closure, should be considered during drug development.

152 The long-term testing should be continued for a sufficient period of time beyond 12 months to
153 cover all appropriate retest periods, and the further accumulated data can be submitted to the
154 FDA during the assessment period of the drug application. [ICH Q1A]

155 The data (from accelerated testing and/or from testing at an intermediate storage condition) may
156 be used to evaluate the impact of short-term excursions outside the label storage conditions such
157 as might occur during shipping. [ICH Q1A]

158 5. Testing Frequency

³The equipment must be capable of controlling temperature to a range of $\pm 2^{\circ}\text{C}$ and relative humidity to $\pm 5\%$ RH. The actual temperatures and humidities should be monitored during stability storage. Short-term spikes due to opening of doors of the storage facility are accepted as unavoidable. The effect of excursions due to equipment failure should be addressed by the applicant and reported if judged to impact stability results. Excursions that exceed these ranges (i.e., $\pm 2^{\circ}\text{C}$ and/or $\pm 5\% \text{RH}$) for more than 24 hours should be described and their impact assessed in the study report.

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159 Frequency of testing should be sufficient to establish the stability characteristics of the drug
160 substance. Testing under the defined long-term conditions will normally be every 3 months over
161 the first year, every 6 months over the second year, and then annually. [ICH Q1A]

162 6. Packaging /Containers

163 The containers to be used in the long-term, real-time stability evaluation should be the same as or
164 simulate the actual packaging used for storage and distribution. [ICH Q1A]

165 7. Evaluation

166 The design of the stability study is to establish a retest period applicable to all future batches of
167 the bulk drug substance manufactured under similar circumstances, based on testing a minimum of
168 three batches of the drug substance and evaluating the stability information (covering as necessary
169 the physical, chemical, and microbiological test characteristics). The degree of variability of
170 individual batches affects the confidence that a future production batch will remain within
171 specifications until the retest date. [ICH Q1A]

172
173 An acceptable approach for quantitative characteristics that are expected to decrease with time is
174 to determine the time at which the 95 percent one-sided confidence limit for the mean degradation
175 curve intersects the acceptable lower specification limit. If analysis shows that the batch to batch
176 variability is small, it is advantageous to combine the data into one overall estimate, and this can
177 be done by first applying appropriate statistical tests (for example, p values for level of
178 significance of rejection of more than 0.25) to the slopes of the regression lines and zero time
179 intercepts for the individual batches. If it is inappropriate to combine data from several batches,
180 the overall retest period may depend on the minimum time a batch may be expected to remain
181 within acceptable and justified limits. [ICH Q1A]

182 The nature of any degradation relationship will determine the need for transformation of the data
183 for linear regression analysis. Usually the relationship can be represented by a linear, quadratic, or
184 cubic function on an arithmetic or logarithmic scale. Statistical methods should be employed to
185 test the goodness of fit of the data on all batches and combined batches (where appropriate) to the
186 assumed degradation line or curve. [ICH Q1A]

187 The data may show so little degradation and so little variability that it is apparent from looking at
188 the data that the requested retest period will be granted. Under the circumstances, it is normally
189 unnecessary to go through the formal statistical analysis; providing a full justification for the
190 omission is usually sufficient. [ICH Q1A]

191 Limited extrapolation may be undertaken of the real-time data beyond the observed range to
192 extend retest period at approval time, particularly where the accelerated data support this.
193 However, this assumes that the same degradation relationship will continue to apply beyond the
194 observed data, and hence the use of extrapolation must be justified in each application in terms of
195 what is known about such factors as the mechanism of degradation, the goodness of fit of any
196 mathematical model, batch size, and existence of supportive data. Any evaluation should cover

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197 not only the assay, but the levels of degradation products and other appropriate attributes. [ICH
198 Q1A]

199 8. Statements/Labeling

200 A storage temperature range may be used in accordance with relevant national/regional
201 requirements. The range should be based on the stability evaluation of the drug substance.
202 Where applicable, specific requirements should be stated, particularly for drug substances that
203 cannot tolerate freezing. The use of terms such as *ambient conditions* or *room temperature* is
204 unacceptable. [ICH Q1A]

205 A retest period should be derived from the stability information. [ICH Q1A]

206 **B. Drug Product**

207 1. General
208

209 The design of the stability protocol for the drug product should be based on the knowledge
210 obtained on the behavior, properties, and stability of the drug substance and the experience gained
211 from clinical formulation studies. The changes likely to occur upon storage and the rationale for
212 the selection of drug product parameters to be monitored should be stated. [ICH Q1A]

213 2. Selection of Batches
214

215 Stability information from accelerated and long-term testing is to be provided on three batches of
216 the same formulation of the dosage form in the container and closure proposed for marketing.
217 Two of the three batches should be at least pilot scale. The third batch may be smaller (e.g.,
218 25,000 to 50,000 tablets or capsules for solid oral dosage forms). The long-term testing should
219 cover at least 12 months' duration at the time of submission. The manufacturing process to be
220 used should meaningfully simulate that to be applied to large-scale production batches for
221 marketing. The process should provide product of the same quality intended for marketing, and
222 meeting the same quality specification to be applied for release of material. Where possible,
223 batches of the finished product should be manufactured using identifiably different batches of the
224 drug substance. [ICH Q1A]

225 Data on laboratory-scale batches are not acceptable as primary stability information. Data on
226 associated formulations or packaging may be submitted as supportive information. The first three
227 production batches manufactured post approval, if not submitted in the original application,
228 should be placed on accelerated and long-term stability studies using the same stability protocols
229 as in the approved drug application. [ICH Q1A]

230 3. Test Procedures and Test Criteria

231 The test parameters should cover those features susceptible to change during storage and likely
232 to influence quality, safety and/or efficacy. Analytical test procedures should be fully validated
233 and the assays should be stability-indicating. The need for replication will depend on the results

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234 of validation studies. [ICH Q1A]

235 The range of testing should cover not only chemical and biological stability, but also loss of
236 preservative, physical properties and characteristics, organoleptic properties, and where required,
237 microbiological attributes. Preservative efficacy testing and assays on stored samples should be
238 carried out to determine the content and efficacy of antimicrobial preservatives. [ICH Q1A]

239 4. Specifications

240 Where applicable, limits of acceptance should relate to the release limits to be derived from
241 consideration of all the available stability information. The shelf-life specifications could allow
242 acceptable and justifiable deviations from the release specifications based on the stability
243 evaluation and the changes observed on storage. They need to include specific upper limits for
244 degradation products, the justification for which should be influenced by the levels observed in
245 material used in preclinical studies and clinical trials. The justification for the limits proposed for
246 certain other tests, such as particle size and/or dissolution rate, will require reference to the results
247 observed for the batch(es) used in bioavailability and/or clinical studies. Any differences between
248 the release and shelf-life specifications for antimicrobial preservatives content should be supported
249 by preservative efficacy testing. [ICH Q1A]

250 5. Storage Test Conditions

251 The length of the studies and the storage conditions should be sufficient to cover storage,
252 shipment and subsequent use (e.g., reconstitution or dilution as recommended in the labeling). See
253 Table 1 below for recommended accelerated and long-term storage conditions and minimum
254 times. Assurance that long-term testing will continue to cover the expected shelf life should be
255 provided. [ICH Q1A]

256 Other storage conditions are allowable if justified. Heat-sensitive drug products should be stored
257 under an alternative lower temperature condition, which will eventually become the designated
258 long-term storage temperature. Special consideration may need to be given to products that
259 change physically or even chemically at lower storage temperatures (e.g., suspensions or
260 emulsions which may sediment, or cream, oils and semi-solid preparations, which may show an
261 increased viscosity). Where a lower temperature condition is used, the 6-month accelerated
262 testing should be carried out at a temperature at least 15°C above its designated long-term
263 storage temperature (together with appropriate relative humidity conditions for that temperature).
264 For example, for a product to be stored long-term under refrigerated conditions, accelerated
265 testing should be conducted at 25°C ± 2°C/60% RH ± 5%. The designated long-term testing
266 conditions will be reflected in the labeling and expiration date. [ICH Q1A]

267 Storage under conditions of high relative humidity applies particularly to solid dosage forms. For
268 drug products such as solutions and suspensions contained in packs designed to provide a
269 permanent barrier to water loss, specific storage under conditions of high relative humidity is not
270 necessary but the same range of temperatures should be applied. Low relative humidity (e.g., 10 -
271 20% RH) can adversely affect products packed in semi-permeable containers (e.g., solutions in

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272 plastic bags, nose drops in small plastic containers), and consideration should be given to
273 appropriate testing under such conditions. [ICH Q1A]

274 **Table 1: Long-Term/Accelerated Testing Conditions**

	Conditions	Minimum time period at submission
275 Long-term testing	25°C ± 2°C/60% RH ± 5%	12 Months
276 Accelerated Testing	40°C ± 2°C/75% RH ± 5%	6 Months

277 Where *significant change* occurs due to accelerated testing, additional testing at an intermediate
278 condition (e.g., 30°C ± 2°C/60% RH ± 5%) should be conducted. *Significant change* at the
279 accelerated conditions is defined as:

- 280 1. A 5 percent potency loss from the initial assay value of a batch.
- 281 2. Any specified degradant exceeding its specification limit.
- 282 3. The product exceeding its pH limits.
- 283 4. Dissolution exceeding the specification limits for 12 capsules or tablets (USP Stage 2).
- 284 5. Failure to meet specifications for appearance and physical properties (e.g., color, phase
285 separation, resuspendability, delivery per actuation, caking, hardness) [ICH Q1A].

286 Should significant change occur at 40°C/75% RH, the initial application should include a
287 minimum of 6 months' data from an ongoing 1-year study at 30°C/60 percent RH; the same
288 significant change criteria shall then apply. [ICH Q1A]

289 If any parameter fails *significant change* criteria during the accelerated stability study, testing of
290 all parameters during the intermediate stability study should be performed.

291 If stability samples have been put into the intermediate condition, but have not been tested, testing
292 these samples may begin as soon as the accelerated study shows significant change in the drug
293 product. Alternatively, the study at the intermediate condition would be started from the initial
294 time point.

295 Where a *significant change* occurs during 12 months of storage at 30°C/60%RH, it may not be
296 appropriate to label the drug product for CRT storage with the proposed expiration dating period
297 even if the stability data from the full long-term studies at 25°C/60%RH appear satisfactory. In
298 such cases, alternate approaches, such as qualifying higher acceptance criteria for a degradant,
299 shorter expiration dating period, refrigerator temperature storage, more protective container
300 and/or closure, modification to the formulation and/or manufacturing process, should be
301 considered during drug development. If CRT storage is ultimately justified, it may be necessary
302 to add to the product labeling a cautionary statement against prolonged exposure at or above
303 30°C.

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304 The long-term testing will be continued for a sufficient period of time beyond 12 months to cover
305 shelf life at appropriate test periods. The further accumulated data should be submitted to the
306 FDA during the assessment period of the drug application. [ICH Q1A]

307 The first three production batches manufactured post approval, if not submitted in the original
308 application, should be placed on accelerated and long-term stability studies using the same
309 stability protocol as in the approved drug application. [ICH Q1A] A minimum of 4 test stations
310 (e.g., 0, 2, 4, and 6 months) are recommended for the 6-month accelerated stability study.

311 6. Stability Storage Conditions not Defined in ICH Q1A

312 The stability sample storage conditions for most dosage forms (e.g., solid oral dosage forms,
313 solids for reconstitution, dry and lyophilized powders in glass vials) are defined in Section V.E. of
314 the ICH Q1A Guidance and in Section II.B.5 of this guidance. However, the stability storage
315 conditions are not indicated in ICH Q1A for certain other drug products including those packaged
316 in semi-permeable containers (except for accelerated studies), products intended to be stored
317 under refrigerator or freezer temperatures, or certain studies on metered dose inhalations (MDIs)
318 and dry powder inhalers (DPIs). Further information about these products and containers is
319 provided in this section.

320 a. Stability Storage Conditions for Drug Products in Semi-Permeable and Permeable
321 Containers

322 For large volume parenterals (LVPs), small volume parenterals (SVPs), ophthalmics, otics, and
323 nasal sprays packaged in semi-permeable containers, such as plastic bags, semi-rigid plastic
324 containers, ampules, vials and bottles with or without droppers/applicators, which may be
325 susceptible to water loss, the recommended stability storage conditions are:

- 326 • Accelerated condition: $40^{\circ}\text{C} \pm 2^{\circ}\text{C}/15\% \text{ RH} \pm 5\%$ (hereafter referred to as $40^{\circ}\text{C}/15\%$
327 RH)[ICH Q1A];
328 • Intermediate condition: $30^{\circ}\text{C} \pm 2^{\circ}\text{C}/40\% \text{ RH} \pm 5\%$ (hereafter referred to as $30^{\circ}\text{C}/40\% \text{ RH}$);
329 • Long-term condition: $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/40\% \text{ RH} \pm 5\%$

330 For liquids in glass bottles, vials, or sealed glass ampules, which provide an impermeable barrier
331 to water loss,

- 332 • Accelerated condition: $40^{\circ}\text{C}/\text{ambient humidity}$ is an acceptable alternative to $40^{\circ}\text{C}/75\% \text{ RH}$;
333 • Intermediate condition: $30^{\circ}\text{C}/\text{ambient humidity}$ is an acceptable alternative to $30^{\circ}\text{C}/60\% \text{ RH}$;
334 • Long-term condition: $25^{\circ}\text{C}/\text{ambient humidity}$ is an acceptable alternative to $25^{\circ}\text{C}/60\% \text{ RH}$.

335 b. Stability Storage Conditions for Drug Products Intended to be Stored at
336 Refrigerator Temperature

- 337 • Accelerated conditions: $25^{\circ}\text{C}/60\% \text{ RH}$, with ambient humidity an acceptable alternative for
338 aqueous products that would not be affected by humidity conditions;
339 • Long-term conditions: $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$, with monitoring, but not control of, humidity.

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340 c. Stability Storage Conditions for Drug Products Intended to be Stored at Freezer
341 Temperature

- 342 • Accelerated conditions: $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ /ambient humidity;
- 343 • Long-term conditions: $-15^{\circ}\text{C} \pm 5^{\circ}\text{C}$.

344 d. Stability Storage Conditions for Some Inhalation Products

345 Additional storage conditions may apply to inhalation powders and suspension inhalation aerosols
346 when significant change in aerodynamic particle size distribution or in dose content uniformity
347 occurs at accelerated conditions (40C/75%RH). (The Agency currently is developing a draft
348 guidance to address chemistry, manufacturing, and controls documentation for MDIs and DPIs.)

349 7. Testing Frequency

350 Frequency of testing should be sufficient to establish the stability characteristics of the drug
351 product. Testing will normally be every 3 months over the first year, every 6 months over the
352 second year, and then annually. Matrixing or bracketing can be used, if justified. [ICH Q1A] A
353 minimum of 4 test stations (e.g., 0, 2, 4, and 6 months) are recommended for the 6-month
354 accelerated stability study.

355 8. Application of ICH Stability Study Storage Conditions to Approved Applications

357 Although the ICH Guidance for *Stability Testing of New Drug Substances and Products* applies
358 only to new molecular entities and associated drug products, applicants may wish to voluntarily
359 switch to the ICH-recommended storage conditions as defined in ICH Q1A and Sections II.A.4.
360 and II.B.5. of this guidance or other FDA-recommended conditions as described in Section II.B.6.
361 of this guidance, as appropriate, for previously approved drug or biologic products. Applicants
362 are not required to make such a switch for either annual stability batches or batches intended to
363 support supplemental changes. Although the following discussions refer only to the ICH
364 conditions, the same recommendations can be applied when a switch to other FDA-recommended
365 conditions is contemplated.

366 Two plans are presented to assist applicants who desire to switch their approved drug products to
367 the ICH-recommended storage conditions. Under each plan, recommendations will be made on
368 how to initiate a switch to the ICH storage testing conditions, select batches, collect data, report
369 results, and proceed if products fail the approved specifications under the ICH conditions.

370 **a. Plan A: Using the ICH Storage Testing Conditions for an Approved Stability**
371 **Protocol**

372 This plan may be most suitable for drug products that have been confirmed to be stable when
373 exposed to the controlled level of humidity on a long-term basis. Only one set of conditions (i.e.,
374 the ICH conditions) and one set of testing for each of the three verification batches, as defined
375 below, are necessary under this plan.

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376 i. Drug Products with an Approved Stability Protocol
377

378 Applicants who have previously performed drug product stability studies under an approved
379 protocol at 25°C, 30°C, or 25-30°C without humidity controls may switch over to the ICH
380 long-term conditions, as defined in V.E. of the ICH Q1A guidance and incorporated in Section
381 II.B. of this guidance, for all of their annual stability studies. A revised stability protocol may be
382 submitted in the annual report, reflecting changes in temperature and humidity to conform with
383 those recommended by the ICH. Any other changes to the stability protocol should be submitted
384 as a prior-approval supplement. Once adopted through an annual report, the ICH conditions
385 should be used to generate stability data for subsequent supplemental changes. Alternatively, the
386 applicant may report the ICH switch in a supplement, which requires stability data, if the
387 supplement occurs before the next scheduled annual report. Data from the first three consecutive
388 annual batches after the switch can be used to verify the previously approved expiration dating
389 period. However, if the applicant wishes to verify product stability under the ICH conditions over
390 a shorter time span, three production batches within one year, instead of three consecutive annual
391 batches, may be studied.

392 ii. Products Without an Approved Stability Protocol

393 Applicants who have previously performed stability studies on a drug product without an
394 approved protocol are required to submit an appropriate protocol under a prior-approval
395 supplement under 21 CFR 314.70(b) or (g) or 601.12(b) (see Section V regarding an Approved
396 Stability Protocol). Upon approval of the protocol, applicants may initiate stability studies on all
397 annual batches under the ICH long-term conditions. Data from the first three consecutive annual
398 batches after the switch can be used to verify the current, or to establish a new, expiration dating
399 period. However, if the applicant wishes to verify product stability under the ICH conditions over
400 a shorter time span, three production batches within one year, instead of three consecutive annual
401 batches, may be studied

402 iii. Stability Data for Supplemental Changes

403 Stability data submitted in support of supplemental changes for an existing drug product may be
404 generated with samples stored at the ICH-recommended accelerated testing conditions, and
405 long-term testing conditions, and, if applicable, intermediate conditions, as described in V.E. of
406 the ICH Q1A guidance (Section II.B. of this guidance) or Section III.B of this guidance.

407 iv. Other Considerations

408 For a moisture-sensitive product, the applicant may wish to explore the possibility of improving
409 the container/closure before embarking on the switch-over to the ICH condition.

410 Although 30°C/60% RH is an acceptable alternative to 25°C/60% RH for long-term studies,
411 these conditions should not be used as the basis for a labeling statement such as “Store at 30°C”
412 or “Store at 15-30°C” to gain marketing advantage.

413 With respect to ongoing stability studies, applicants may carry them to completion under the

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414 previously approved conditions or may, for practical or economic reasons, choose to make an
415 immediate switch to ICH conditions and report the change in the next annual report.

416 v. Data Submission to FDA

417 *Satisfactory data:*

418 If the stability data generated on the first three annual batches after the switch to the
419 ICH-recommended long-term testing conditions using an approved protocol, as defined
420 above, support the previously approved expiration dating period under the non-ICH
421 conditions, the data can be submitted in the next annual report, and the current expiration
422 dating period can be retained.

423 *Unsatisfactory data:*

424 If the stability data under the ICH conditions fall outside the specifications established for the
425 previously approved expiration dating period, the applicant should perform an investigation to
426 determine the probable cause of the failure in accordance with CGMP regulations under 21
427 CFR 211.192. Additionally, the applicant should submit an NDA Field-Alert Report in
428 accordance with 21 CFR 314.81(b)(1)(ii) or an error and accident report for a biological
429 product under 21 CFR 600.14. A recall of the corresponding product in the market place may
430 also be necessary. If it is determined that the ICH storage conditions, particularly the added
431 humidity, is the cause for the stability failure, the applicant may shorten the expiration dating
432 period in a changes-being-effected supplement while retaining the ICH storage condition.
433 Subsequently, if justified, the applicant may request an approval for a revision of the product
434 specifications and for reinstating the previously approved expiration dating period under the
435 non-ICH conditions through a prior-approval supplement. Other measures (e.g., more
436 protective container/closure or product reformulation) may be considered through a
437 prior-approval supplement.

438 Alternatively, the applicant may, after careful consideration of all aspects, request for a return
439 to the previous storage conditions in a changes-being-effected supplement if justification,
440 including all related data and investigational results, is provided.

441 **b. Plan B: Using the ICH Conditions under an Alternate Protocol**

442 An alternative to Plan A is to conduct two side-by-side studies by simultaneously placing samples
443 from the same batch of drug product under the ICH conditions as well as the previously approved
444 storage condition. The protocol containing the ICH storage conditions is considered an
445 alternative to the approved protocol. This plan may prove to be particularly useful if the drug
446 product is believed to be moisture-sensitive.

447
448 i. Products with an Approved Stability Protocol

449
450 Applicants may initiate stability studies under the ICH-recommended long-term testing conditions,
451 in addition to the previously approved conditions at 25°C, 30°C, or 25-30°C without humidity

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452 controls, for three consecutive annual batches. Data from these annual batches under the ICH
453 conditions should be used to verify the current expiration dating period. However, if the applicant
454 wishes to verify the ICH conditions over a shorter time span, three production batches within one
455 year or less may be selected, instead of three consecutive annual batches.

456 ii. Products without an Approved Stability Protocol

457 Applicants who have previously performed stability studies on a drug product without an
458 approved protocol should submit an appropriate protocol as a prior-approval supplement. This
459 protocol should contain 25°C/ambient humidity as the primary long-term storage testing
460 conditions and the ICH long-term conditions, as the alternative, as well as the IC-recommended
461 accelerated testing conditions. Upon approval of the protocol, applicants may initiate stability
462 studies on three consecutive annual batches at both 25°C/ambient humidity and 25°C/60% RH or
463 25°C/40% RH. Data from these annual batches under the ICH conditions can be used to verify
464 the current, or to establish a new, expiration dating period.

465 iii. Other Considerations

466 Same as in Plan A.

467 iv. Protocol Revisions

468
469 *Products with an approved stability protocol:*

470 Applicants who have an approved stability protocol may submit the alternate stability protocol
471 in the annual report, reflecting the temperature and humidity as recommended by the ICH.
472 Other changes to the stability protocol generally should be submitted in a prior-approval
473 supplement, unless the changes are to comply with the current compendium.

474 Once adopted as an alternate protocol through an annual report, the ICH conditions can be
475 used, in parallel with the previously approved conditions, to generate stability data for
476 subsequent supplemental changes. Alternatively, the applicant may report the alternative ICH
477 conditions in a supplement, which requires stability data, if the supplement occurs before the
478 next scheduled annual report.

479 If the complete stability data generated on the first three annual batches under the ICH
480 long-term conditions using an approved alternate protocol (as defined above) support the
481 previously approved expiration dating period under the non-ICH conditions, the alternate
482 stability protocol can be adopted as the primary stability protocol through an annual report.

483 *Products without an approved stability protocol:*

484 For applications that do not contain an approved stability protocol as defined above, a new or
485 revised stability protocol may be submitted in a prior-approval supplement marked *expedited*
486 *review requested*. This protocol should encompass 25°C/ambient humidity as the primary
487 long-term storage conditions and the ICH long-term conditions, as the alternate, as well as

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488 accelerated stability storage conditions, as defined by the ICH Guidance and above, and other
489 recommendations described in this guidance. Upon approval of the protocol, stability studies
490 may be initiated on annual batches and batches intended to support supplemental changes.

491 v. Stability Data for Supplemental Changes

492 Applicants may provide stability data in support of postapproval supplemental changes with
493 samples stored at the ICH-recommended accelerated testing conditions and long-term testing
494 conditions, both previously approved and ICH, as well as, if applicable, intermediate conditions.
495 See Change in Stability Protocol (Section IX.J.) for the recommended filing mechanism.

496 vi. Data Submission

497 *Satisfactory data:*

498 If the complete stability data generated on the first three annual batches under the ICH
499 long-term conditions using an approved alternate protocol support the previously approved
500 expiration dating period under the non-ICH conditions, the data can be submitted in the
501 annual report and the current expiration dating period can be retained.

502 *Unsatisfactory data*

503 If the stability data under the ICH conditions fall outside the acceptance criteria while data
504 from the parallel study under the previously approved conditions or 25°C/ambient humidity,
505 whichever applies, are satisfactory during the previously approved expiration dating period,
506 and the added humidity is determined to be the cause for the stability failure, the product will
507 still be considered to be in compliance with the regulatory specifications approved in the
508 application. If the applicant decides to adopt the ICH conditions, a changes-being-effected
509 supplement with shortened expiration dating period or a prior-approval supplement with
510 revised product specifications may be submitted where justified. Other measures (e.g., more
511 protective container/closure or product reformulation) may be considered through a
512 prior-approval supplement.

513 Alternatively, after careful consideration of all aspects, the applicant may decide not to pursue
514 the switch-over to the ICH conditions for the product. The applicant may eliminate the
515 alternate stability protocol in the next annual report if a full explanation, including all related
516 data and investigational results, is provided.

517 In the case where the product fails to meet the specifications under the non-ICH conditions,
518 irrespective of whether it also fails under the ICH conditions, a thorough investigation in
519 accordance with CGMP should be performed and appropriate corrective actions should be
520 taken, including a Field-Alert Report and recall of the affected product from the market place
521 if warranted.

522 9. Packaging Materials [ICH Q1A]

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523 The testing should be carried out in the final packaging proposed for marketing. Additional
524 testing of the unprotected drug product can form a useful part of the stress testing and package
525 evaluation, as can studies carried out in other related packaging materials in supporting the
526 definitive pack(s).

527 10. Evaluation [ICH Q1A]

528 A systematic approach should be adopted in the presentation of the evaluation of the stability
529 information, which should cover, as necessary, physical, chemical, biological and microbiological
530 quality characteristics, including particular properties of the dosage form (for example, dissolution
531 rate for oral solid dose forms).

532 The design of the stability study is to establish a shelf-life and label storage instructions applicable
533 to all future batches of the dosage form manufactured and packed under similar circumstances
534 based on testing a minimum of three batches of the drug product. The degree of variability of
535 individual batches affects the confidence that a future production batch will remain within
536 specifications until the expiration date.

537 An acceptable approach for quantitative characteristics that are expected to decrease with time is
538 to determine the time at which the 95 percent one-sided confidence limit for the mean degradation
539 curve intersects the acceptable lower specification limit. If analysis shows that the batch-to-batch
540 variability is small, it may be advantageous to combine the data into one overall estimate by first
541 applying appropriate statistical tests (e.g., p values for level of significance of rejection of more
542 than 0.25) to the slopes of the regression lines and zero time intercepts for the individual batches.
543 If combining data from several batches is inappropriate, the overall retest period may depend on
544 the minimum time a batch may be expected to remain within acceptable and justified limits.

545 The nature of the degradation relationship will determine the need for transformation of the data
546 for linear regression analysis. Usually the relationship can be represented by a linear, quadratic, or
547 cubic function of an arithmetic or logarithmic scale. Statistical methods should be employed to
548 test the goodness of fit of the data on all batches and combined batches (where appropriate) to the
549 assumed degradation line or curve.

550 Where the data show so little degradation and so little variability that it is apparent from looking
551 at the data that the requested shelf life will be granted, it is normally unnecessary to go through
552 the formal statistical analysis; but a justification for the omission should be provided.

553 Limited extrapolation may be taken of the real-time data beyond the observed range to extend
554 expiration dating at approval time, particularly where the accelerated data support this. However,
555 this assumes that the same degradation relationship will continue to apply beyond the observed
556 data, and hence the use of extrapolation must be justified in each application in terms of what is
557 known about such factors as the mechanism of degradation, the goodness of fit of any
558 mathematical model, batch size, and existence of supportive data.

559 Any evaluation should cover not only the assay, but also the levels of degradation products and

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560 appropriate attributes. Where appropriate, attention should be paid to reviewing the adequacy of
561 the mass balance, different stability, and degradation performance.

562 The stability of the drug product after reconstituting or diluting according to labeling should be
563 addressed to provide appropriate and supportive information.

564 See Section VIII.N. for additional information on drug products which are reconstituted or
565 diluted.

566 11. Statements/Labeling

567 A storage temperature range may be used in accordance with FDA regulations. The range should
568 be based on the stability evaluation of the drug product. Where applicable, specific requirements
569 should be stated, particularly for drug products that cannot tolerate freezing.

570 The use of terms such as *ambient conditions* or *room temperature* is unacceptable.

571 There should be a direct linkage between the label statement and the demonstrated stability
572 characteristics of the drug product.

573 A single set of uniform storage statements (USSs) for NDAs, ANDAs, PLAs and BLAs is
574 recommended to avoid different labeling storage statements for products stored under controlled
575 room temperature conditions. The storage statements and storage conditions provided in this
576 section of the guidance are intended to be standardized and harmonized with the CRT definition
577 in the USP and the recommendations in the ICH guidance.

578 a. Room Temperature Storage Statements

579 i. Liquid Dosage Forms in Semi-Permeable Containers
580

581 The recommended storage statement for LVPs, SVPs, ophthalmics, otics and nasal sprays
582 packaged in semi-permeable containers, such as plastic bags, semi-rigid plastic containers,
583 ampules, vials and bottles with or without droppers/applicators, that may be susceptible to water
584 loss but have been demonstrated to be stable at 25°C ± 2°C/40% or 60% RH ± 5% (or 30°C ±
585 2°C/40% or 60% RH ± 5%); at 25°C/NMT 40% or 30°C/NMT 40% RH; or 30°C, 25-30°C, or
586 25°C without humidity controls, is:

587 **Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F)**
588 [see USP Controlled Room Temperature]

589 For sterile water for injection (WFI) and LVP solutions of inorganic salts packaged in
590 semi-permeable containers (e.g., plastic bags) the following statement may be used on the
591 immediate container labels:

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592 **Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F)**
593 [see USP Controlled Room Temperature]
594 (see insert for further information)

595 and the following statement may be used in the “How Supplied” section of the package insert:

596 **Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F)**
597 [see USP Controlled Room Temperature]
598 **Brief exposure to temperatures up to 40°C/104°F may be tolerated provided the**
599 **mean kinetic temperature does not exceed 25°C (77°F).**
600 **However, such exposure should be minimized.**

601 LVP solutions packaged in a semi-permeable container (e.g., a plastic bag) and containing simple
602 organic salts (e.g., acetate, citrate, gluconate, and lactate, and dextrose 10 percent or less) may be
603 labeled as above, provided there are adequate stability data (at least 3 months’ at 40°C ±
604 2°C/15% RH ± 5% or 40°C/NMT 20% RH) to support such labeling.

605
606 ii. All Other Dosage Forms

607 For all other dosage forms (e.g., solid oral dosage forms, dry powders, aqueous liquid, semi-solid
608 and suspension dosage forms) that have been demonstrated to be stable at the ICH-recommended
609 conditions (25°C ± 2°C/60% RH ± 5%, or 30°C/60% RH ± 5%) or at non-ICH conditions, such
610 as 30°C, 25-30°C, or 25°C without humidity controls and intended to be stored at room
611 temperature, the recommended labeling statement is:

612 **Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F)**
613 [see USP Controlled Room Temperature]

614 iii. Where Space on the Immediate Container is Limited

615 Where an abbreviated labeling statement is necessary because space on the immediate container is
616 limited, either of the following statements is acceptable provided the full labeling statement, as
617 shown above, appears on the outer carton and in the package insert:

618 **Store at 25°C (77°F); excursions 15-30°C (59-86°F)**
619 **Store at 25°C (77°F) (see insert)**

620 b. Refrigerator Storage Statement

621 For a drug product demonstrated to be stable at 5°C ± 3°C, 2-5°C, or 2-8°C with or without

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622 humidity control and which is intended to be stored at refrigerator temperature, the recommended
623 storage statement for labeling may be one of the following:

624 **Store in a refrigerator, 2-8°C (36-46°F)**
625 **Store refrigerated, 2-8°C (36-46°F)**

626
627 Where an abbreviated labeling statement is necessary because space on the immediate container is
628 limited, the following statement is acceptable, provided one of the full labeling statements, as
629 shown above, appears on the outer container and in the package insert:

630 **Refrigerate (see insert)**

631 c. Room Temperature and/or Refrigerator Storage Statement

632 For a drug product demonstrated to be stable both at 25°C ± 2°C/60% RH ± 5% and at
633 refrigerator temperature, either/or both of the room temperature and refrigerator labeling
634 statements, as described above, are acceptable, depending on the storage conditions intended for
635 the product. A statement such as “store at 2-25°C” is not recommended.

636 d. Additional Cautionary Statements

637 If warranted, additional cautionary statements to protect a drug product from excessive heat,
638 light, humidity, freezing, and other damaging conditions, should be included on the container label
639 and the package insert. If the space on the container label is too limited to display all the
640 recommended statements in detail, a reference to the package insert for further information (e.g.,
641 *see insert*) is recommended. The uniform storage statements and stability conditions are
642 summarized in Tables 2 and 3, respectively.

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643

Table 2: Summary of Uniform Storage Statements in Drug Product Labeling

		Recommended Storage Statement in Drug Product Labeling	
		Full	Abbreviated
Intended storage conditions for drug product	Room Temperature	Store at 25°C (77°F) excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]	Store at 25°C (77°F) excursions 15-30°C (59-86°F) or Store at 25°C (77°F) (see insert)
	Refrigerator Temperature	Store in a refrigerator, 2-8°C (36-46°F) or Store refrigerated	Refrigerate (see insert)

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Table 3: Conditions under which Product has been Shown to be Stable to Apply Uniform Storage Statements

Intended storage conditions for drug product	Room Temperature		Refrigerator Temperature
Type of product	LVP in a plastic bag ^a or Aqueous Solution in a LDPE bottle or prefilled syringe	All other types	All drug products (as appropriate)
Conditions under which product has been shown to be stable	25°C ± 2°C/60% RH ± 5% 30°C ± 2°C/40% RH ± 5% 25°C/NMT 40% RH 30°C/NMT 40% RH or 25°C, 30°C or 25-30°C and ambient humidity	25°C ± 2°C /60% RH ± 5% 30°C/60% RH ± 5% or 25°C, 30°C or 25-30°C and ambient humidity	5°C ± 3°C 2-5°C or 2-8°C

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^a See Section II.B.11.a. for additional information on sterile water for injection and LVPs containing inorganic salts or simple organic salts.

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662 e. Other Considerations

663 The applicant may wish to include the definition of USP CRT in its entirety in the package insert
664 to provide easy reference.

665 f. Implementation of the USSs in Labeling for New Product Applications

666 The recommended storage statements in labeling should be adopted for new or pending NDA,
667 ANDA, BLA or PLA products. For applications approved prior to the publication of the
668 guidance, the recommended storage statements should be adopted through the annual report
669 mechanism at the next printing opportunity if desired, but within three years of the date of the
670 final guidance. With respect to room temperature storage statements for already approved
671 products, new stability studies under the ICH conditions are not required to adopt the
672 recommended room temperature labeling statements, provided the products have been
673 demonstrated to be stable through expiry under one of the following controlled temperatures:
674 30°C, 25-30°C, 25°C and at ambient humidity.

675 **C. New Dosage Forms [ICH Q1C]**

676 A new dosage form is defined as a drug product that is a different pharmaceutical product type,
677 but contains the same active substance as included in an existing drug product approved by the
678 FDA.

679 New dosage forms include products of different administration route (e.g., oral, when the original
680 new drug product was a parenteral), new specific functionality/delivery system (e.g., modified
681 release tablet, when the original new drug product was an immediate release tablet, and different
682 dosage forms of the same administration route (e.g., capsule to tablet, solution to suspension).

683 Stability protocols for new dosage forms should follow the guidance in the ICH Q1A in principle.
684 However, a reduced stability database at submission time (e.g., 6 months' accelerated and 6
685 months' long-term data from ongoing studies) may be acceptable in certain justified cases.

686 **D. Other NDAs**

687 Stability protocols for new combination products or new formulations (which require clinical data
688 for approval) should follow the guidance in the ICH Q1A in principle. However, a reduced
689 stability database at submission time (e.g., 6 months' accelerated and 6 months' data from
690 ongoing studies at the long-term condition) may be acceptable in certain justified cases, such as
691 when there is a significant body of information on the stability of the drug product and the dosage
692 form.

693 **III. STABILITY TESTING FOR ABBREVIATED NEW DRUG APPLICATIONS**

694 Much of the general information provided in this guidance is applicable to abbreviated new drugs
695 (ANDAs). However, depending upon the availability of significant information on, and the

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696 complexity of, these drug products/dosage forms, the amount of information necessary to support
697 these applications may vary from that proposed for NDAs. This section is intended to provide
698 specific recommendations on abbreviated applications.

699 **A. Drug Substance Stability Data Submission**

700 For drug products submitted under an ANDA, including antibiotics, supporting information may
701 be provided directly to the drug product ANDA or by reference to an appropriately referenced
702 drug master file (DMF). Publications may be provided or referenced as supportive information.
703 For ANDA bulk drug substances, stability data should be generated on a minimum of one pilot-
704 scale batch. All batches should be made using equipment of the same design and operating
705 principle as the manufacturing-scale production equipment with the exception of capacity. For
706 ANDA bulk drug substances produced by fermentation, stability data should be provided on three
707 production batches, at least two of which should be generated from different starter cultures.
708

709 **B. Drug Substance Testing**

710 A program for stability assessment may include storage at accelerated, long-term, and, if
711 applicable, intermediate stability study storage conditions (refer to IV.G. of the ICH Q1A
712 Guidance and Section II.A. of this guidance). Stability samples should be stored in the bulk
713 storage container equivalent (e.g., same composition and type of container, closure and liner, but
714 smaller in size).

715 If not previously generated or available by reference, stress testing studies should be conducted to
716 establish the inherent stability characteristics of the drug substance, and support the suitability of
717 the proposed analytical procedures. The detailed nature of the studies will depend on the
718 individual drug substance, type of drug product and available supporting information. Any
719 necessary testing may be carried out as described in Section II.A.

720 **C. Drug Product**

721 Original ANDAs should contain stability data generated under the long-term and accelerated
722 stability storage conditions delineated in V.E. of the ICH Q1A guidance (Section II.B. of this
723 guidance). The data package for ANDAs (e.g., number of batches, length of studies needed at
724 submission and at approval, and accelerated, intermediate and long-term stability data) should be
725 based on several factors, including the complexity of the dosage form, the existence of a
726 significant body of information for the dosage form, and the existence of an approved application
727 for a particular dosage form.

728 **D. ANDA Data Package Recommendations**

729 For *Simple Dosage Forms* the following stability data package is recommended:

- 730 • Accelerated stability data at 0, 1, 2, and 3 months. A tentative expiration dating period of up
731 to 24 months will be granted based on satisfactory accelerated stability data unless not
732 supported by the available long-term stability data.

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- 733 • Long-term stability data (available data at the time of original filing and subsequent
734 amendments).
735 • A minimum of one batch; pilot scale.
736 • Additional stability studies (12 months at the intermediate conditions, or long-term data
737 through the proposed expiration date) if *significant change* is seen after 3 months during the
738 accelerated stability study. The tentative expiration dating period will be determined based on
739 the available data from the additional study.

740 **E. Exceptions to the ANDA Data Package Recommendations**

741 The following may be considered exceptions to the general ANDA recommendations:

- 742 • Complex dosage forms, such as modified-release products, transdermal patches, metered-dose
743 inhalers.
744 • Drug products without a significant body of information.
745 • New dosage forms submitted through the ANDA suitability petition process (Q1C
746 applications).
747 • Other exceptions may exist and should be discussed with the Office of Generic Drugs.

748 An ANDA that is determined to be one of the above categories should contain a modified ICH
749 Q1A stability data package, including:

- 750 • 3-month accelerated stability studies.
751 • Long-term stability studies (available data at the time of original filing and subsequent
752 amendments). The expiration dating period for complex dosage forms will be determined
753 based on available long-term stability data submitted in the application.
754 • A minimum of three batches manufactured in accordance with the ICH Q1A batch size
755 recommendations (refer to V.B. of the ICH Q1A guidance and Section II.B. of this guidance).
756 • Additional stability studies (12 months at the intermediate conditions or long-term stability
757 testing through the proposed expiration date) if significant change is seen after 3 months
758 during the accelerated stability studies (the tentative expiration dating period will be
759 determined based on the available data from the additional studies).

760 **F. Data Package for Approval**

761 Full-term stability testing of the primary stability batch(es) is suggested. However, in the absence
762 of full-term stability data for the drug product, adequate accelerated stability data combined with
763 available long-term data can be used as the basis for granting a tentative expiration dating period.
764 The batch(es) used for stability testing should comply fully with the proposed specifications for
765 the product and be packaged in the market package, and the release assay should be within
766 reasonable variation (taking into account inherent assay variability) from the labeled strength or
767 theoretical strength of the reference listed drug. If formulated with an overage, the overage
768 should be justified as necessary to match that of the reference listed drug.

769 Other supportive stability data may be submitted on drug product batches that may or may not
770 meet the above criteria. Data on relevant research batches, investigational formulations, alternate

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771 container/closure systems, or from other related studies may also be submitted to support the
772 stability of the drug product. The supportive stability data should be clearly identified.

773 **G. Stability Study Acceptance**

774 If the results are satisfactory, a tentative expiration dating period of up to 24 months at the labeled
775 storage conditions may be granted. Where data from accelerated studies are used to project a
776 tentative expiration dating period that is beyond a date supported by actual long-term studies on
777 production batches, the application should include a commitment to conduct long-term stability
778 studies on the first three production batches and annual batches until the tentative expiration
779 dating period is verified, or the appropriate expiration dating period is determined. Extension of
780 the tentative expiration dating period should be based on data generated on at least three
781 production batches tested according to the approved protocol outlined in the stability
782 commitment. Reporting of the data should follow Section VI. of this guidance.

783 ANDAs withdrawn prior to publication of this guidance should not normally have to include
784 stability data in conformance with the guidance upon resubmission if the original application was
785 withdrawn due to non-stability related issues. However, if new stability studies are conducted to
786 support the submission, such studies should be conducted as recommended in the guidance.

787 **IV. STABILITY TESTING FOR INVESTIGATIONAL NEW DRUG APPLICATIONS**

788 Much of the following information is taken from the guidance for industry, *Content and Format*
789 *of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including*
790 *Well-Characterized, Therapeutic Biotechnology-derived Products* (November 1995).

791 The regulation at 312.23(a)(7) emphasizes the graded nature of manufacturing and controls
792 information. Although in each phase of the investigation, sufficient information should be
793 submitted to ensure the proper identification, quality, purity, and strength of the investigational
794 drug, the amount of information needed to achieve that assurance will vary with the phase of the
795 investigation, the proposed duration of the investigation, the dosage form, and the amount of
796 information otherwise available. Therefore, although stability data are required in all phases of
797 the IND to demonstrate that the new drug substance and drug product are within acceptable
798 chemical and physical limits for the planned duration of the proposed clinical investigation, if very
799 short-term tests are proposed, the supporting stability data can be correspondingly very limited.

800 It is recognized that modifications to the method of preparation of the new drug substance and
801 dosage form, and even changes in the dosage form itself, are likely as the investigation progresses.
802 In an initial phase 1 CMC submission, the emphasis should generally be placed on providing
803 information that will allow evaluation of the safety of subjects in the proposed study. The
804 identification of a safety concern or insufficient data to make an evaluation of safety are the only
805 reasons for placing a trial on clinical hold based on the CMC section.

806 **A. Phase 1**

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807 Information to support the stability of the drug substance during the toxicologic studies and the
808 proposed clinical study(ies) should include the following: a brief description of the stability study
809 and the test methods used to monitor the stability of the drug substance and preliminary tabular
810 data based on representative material. Neither detailed stability data nor the stability protocol
811 need to be submitted.

812 Information to support the stability of the drug product during the toxicologic studies and the
813 proposed clinical study(ies) should include the following: a brief description of the stability study
814 and the test methods used to monitor the stability of the drug product packaged in the proposed
815 container/closure system and storage conditions and preliminary tabular data based on
816 representative material. Neither detailed stability data nor the stability protocol need to be
817 submitted.

818 When significant decomposition during storage cannot be prevented, the clinical trial batch of
819 drug product should be retested prior to the initiation of the trial and information should be
820 submitted to show that it will remain stable during the course of the trial. This information should
821 be based on the limited stability data available when the trial starts. Impurities that increase
822 during storage may be qualified by reference to prior human or animal data.

823 **B. Phase 2**

824 Development of drug product formulations during phase 2 should be based in part on the
825 accumulating stability information gained from studies of the drug substance and its formulations.

826 The objectives of stability testing during phases 1 and 2 are to evaluate the stability of the
827 investigational formulations used in the initial clinical trials, to obtain the additional information
828 needed to develop a final formulation, and to select the most appropriate container and closure
829 (e.g., compatibility studies of potential interactive effects between the drug substance(s) and other
830 components of the system). This information should be summarized and submitted to the IND
831 during phase 2. Stability studies on these formulations should be well underway by the end of
832 Phase 2. At this point the stability protocol for study of both the drug substance and drug
833 product should be defined, so that stability data generated during phase 3 studies will be
834 appropriate for submission in the drug application.

835 **C. Phase 3**

836 In stability testing during phase 3 IND studies, the emphasis should be on testing final
837 formulations in their proposed market packaging and manufacturing site based on the
838 recommendations and objectives of this guidance. It is recommended that the final stability
839 protocol be well defined prior to the initiation of phase 3 IND studies. In this regard,
840 consideration should be given to establish appropriate linkage between the preclinical and clinical
841 batches of the drug substance and drug product and those of the primary stability batches in
842 support of the proposed expiration dating period. Factors to be considered may include, for
843 example, source, quality and purity of various components of the drug product, manufacturing
844 process of and facility for the drug substance and the drug product, and use of same containers

845 and closures.

846 **V. APPROVED STABILITY PROTOCOL**

847 **A. Stability Protocol**

848 An *approved stability protocol* is a detailed plan described in an approved application that is used
849 to generate and analyze stability data to support the retest period for a drug substance or the
850 expiration dating period for a drug product. It also may be used in developing similar data to
851 support an extension of that retest or expiration dating period via annual reports under 21 CFR
852 314.70(d)(5). If needed, consultation with FDA is encouraged prior to the implementation of the
853 stability protocol.

854 To ensure that the identity, strength, quality, and purity of a drug product are maintained
855 throughout its expiration dating period, stability studies should include the drug product packaged
856 in the proposed containers and closures for marketing as well as for physician and/or promotional
857 samples. The stability protocol may also include an assessment of the drug product in bulk
858 containers to support short-term storage prior to packaging in the market container.

859 The stability protocol should include methodology for each parameter assessed during the
860 stability evaluation of the drug substance and the drug product. The protocol should also address
861 analyses and approaches for the evaluation of results and the determination of the expiration
862 dating period, or retest period. The stability-indicating methodology should be validated by the
863 manufacturer and described in sufficient detail to permit validation and/or verification by FDA
864 laboratories.

865
866 The stability protocol for both the drug substance and the drug product should be designed in a
867 manner to allow storage under specifically defined conditions. For the drug product, the protocol
868 should support a labeling storage statement at CRT, refrigerator temperature, or freezer
869 temperature. See Sections II.B.5 and 6.

870 A properly designed stability protocol should include the following information:

- 871 • Technical grade and manufacturer of drug substance and excipients
- 872 • Type, size, and number of batches
- 873 • Type, size, and source of containers and closures
- 874 • Test parameters
- 875 • Test methods
- 876 • Acceptance criteria
- 877 • Test time points
- 878 • Test storage conditions
- 879 • Container storage orientations
- 880 • Sampling plan
- 881 • Statistical analysis approaches and evaluations
- 882 • Data presentation
- 883 • Retest or expiration dating period (proposed or approved)

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- 884 • Stability commitment

885 The use of alternative designs, such as bracketing and matrixing, may be appropriate (see Sections
886 VII.G. and H.).

887 At the time of a drug application approval, the applicant has probably not yet manufactured the
888 subject drug product repeatedly on a production scale or accrued full long-term data. The
889 expiration dating period granted in the original application is based on acceptable accelerated
890 data, statistical analysis of available long-term data, and other supportive data for an NDA, or on
891 acceptable accelerated data for an ANDA. It is often derived from pilot-scale batches of a drug
892 product or from less than full long-term stability data. An expiration dating period assigned in this
893 manner is considered tentative until confirmed with full long-term stability data from at least three
894 production batches reported through annual reports. The stability protocol approved in the
895 application is then crucial for the confirmation purpose.

896 **B. Stability Commitment**

897 A stability commitment is acceptable when there are sufficient supporting data to predict a
898 favorable outcome with a high degree of confidence, such as when an application is approved
899 with stability data available from pilot-plant batches, when a supplement is approved with data
900 that do not cover the full expiration dating period, or as a condition of approval. This
901 commitment constitutes an agreement to:

- 902 1. Conduct and/or complete the necessary studies on the first three production batches and
903 annual batches thereafter of each drug product, container, and closure according to the
904 approved stability protocol through the expiration dating period.
- 905 2. Submit stability study results at the time intervals and in the format specified by the FDA,
906 including the annual batches.
- 907 3. Withdraw from the market any batches found to fall outside the approved specifications for
908 the drug product. If the applicant has evidence that the deviation is a single occurrence that
909 does not affect the safety and efficacy of the drug product, the applicant should immediately
910 discuss it with the appropriate chemistry team and provide justification for the continued
911 distribution of that batch. The change or deterioration in the distributed drug or biological
912 product must be reported under 21 CFR 314.81(b)(1)(ii) or 21 CFR 601.14, respectively.

913 For postapproval changes, items 2 and 3 remain the same and item 1 becomes:

- 914 1. Conduct and/or complete the necessary studies on the appropriate number of batches. The
915 amount of stability data supplied will depend on the nature of the change being made.
916 Applicants may determine the appropriate data package by consulting the PostApproval
917 Changes section of this guidance (Section IX.) and in consultation with the appropriate
918 chemistry review team.

919 The approved stability protocol should be revised as necessary to reflect updates to USP

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920 monographs or the current state-of-the-art regarding the type of parameters monitored,
921 acceptance criteria of such parameters, and the test methodology used to assess such parameters.
922 However, other modifications are discouraged until the expiration dating period granted at the
923 time of approval has been confirmed by long-term data from production batches. Once a
924 sufficient database is established from several production batches to confirm the originally
925 approved expiration dating period, it may be appropriate to modify the stability protocol. See
926 Section IX.J.

927 **VI. REPORTING STABILITY DATA**

928 **A. General**

929 Stability data should be included in the application (NDA, ANDA, BLA, PLA, IND, supplement)
930 they are intended to support. The extent of stability data expected at the time of submission is
931 discussed at length throughout this guidance. Additional data from ongoing studies and regular
932 annual batches should be included in the application's annual report.

933 Annual reports should include new or updated stability data generated in accordance with the
934 approved stability protocol. These data may include accelerated and long-term studies for each
935 product to satisfy the standard stability commitment made in the original or supplemental
936 application, including the annual batch(es), and to support postapproval changes. The data should
937 be presented in an organized, comprehensive, and cumulative format.

938 **B. Content of Stability Reports**

939 It is suggested that stability reports include the following information and data to facilitate
940 decisions concerning drug product stability:

941 1. General Product Information

- 942 • Name, source, manufacturing sites, and date of manufacture of drug substance and drug or
943 biological product.
944 • Dosage form and strength, including formulation. (The application should provide a table of
945 specific formulations under study. When more than one formulation has been studied, the
946 formulation number is acceptable.)
947 • Composition, type, source, size, and adequate description of container and closure. Stuffers,
948 seals, and desiccants should also be identified.

949 2. Specifications and Test Methodology Information

- 950 • Physical, chemical, and microbiological attributes and regulatory specifications (or specific
951 references to NDA, BLA, PLA, or USP).
952 • Test methodology used (or specific reference to IND, ANDA, NDA, BLA, PLA prior
953 submissions, or USP) for each sample tested.
954 • Information on accuracy, precision, and suitability of the methodology (cited by reference to

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- 955 appropriate sections).
- 956 • Where applicable, a description of the potency test(s) for measuring biological activity,
- 957 including specifications for potency determination.

958 3. Study Design and Study Conditions

- 959 • Description of the sampling plan, including:
- 960 • Batches and number selected.
- 961 • Container and closures and number selected.
- 962 • Number of dosage units selected and whether tests were conducted on individual units or
- 963 on composites of individual units.
- 964 • Sampling time points.
- 965 • Testing of drug or biological products for reconstitution at the time of reconstitution (as
- 966 directed on the labeling) as well as through their recommended use periods.
- 967 • Expected duration of the study.
- 968 • Conditions of storage of the product under study (e.g., temperature, humidity, light, container
- 969 orientation).

970 4. Stability Data/Information

- 971 • Batch number (research, pilot, production) and associated manufacturing date.
- 972 • For antibiotic drug products, the age of the bulk active drug substance(s) used in
- 973 manufacturing the batch.
- 974 • Analytical data, source of each data point, and date of analysis (e.g., batch, container,
- 975 composite, etc). Pooled estimates may be submitted if individual data points are provided.
- 976 • Individual data as well as mean and standard deviation should be reported.
- 977 • Tabulated data by storage condition.
- 978 • Summary of information on previous formulations during product development. This
- 979 summary may be referenced (if previously submitted) and should include other containers and
- 980 closures investigated.

981 5. Data Analysis

982 The following data analysis of quantitative parameters should be provided:

- 983 • Evaluation of data, plots, and/or graphics.
- 984 • Documentation of appropriate statistical methods and formulas used.
- 985 • Results of statistical analysis and estimated expiration dating period.
- 986 • Results of statistical tests used in arriving at microbiological potency estimates.

987 6. Conclusions

- 988 • Proposed expiration dating period and its justification.
- 989 • Regulatory specifications (establishment of acceptable minimum potency at the time of initial
- 990 release for full expiration dating period to be warranted).

991 **C. Formatting Stability Reports**

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992 Submitted information should be cumulative and in tabular form. Examples are provided on the
993 following list and in Table 4.

994 **Summary Of Stability Studies For Drug Product X**

995	Study Number	Container Composition/Supplier
996	Drug Product Batch #/Control #*, **	Closure Composition/Supplier
997	Formulation Code/No	Seal/Supplier
998	Dosage and Strength	Mfg/Site/Date
999	Batch Type and Size	Packager/Site/Date
1000	Storage Conditions	Location of Data in Application
1001	Drug Substance Mfg/Site/Batch#	Specs Failures
1002	Length of Study	Reporting Period
1003	*Batches Used in Clinical Studies and Biostudies (Specify)	
1004	**Batches of Different Formulation	

1005 **Table 4: Model Stability Data Presentation**

1006 Summary of Stability Studies for Drug Product X

- 1007 Product Name
- 1008 Study Number
- 1009 Formulation Code/Number
- 1010 Dosage and Strength
- 1011 Drug Product Batch Number/Control Number^{a,b}
- 1012 Batch Type and Size
- 1013 Drug Product Manufacturer/Site/Date
- 1014 Drug Substance Manufacturer/Site/Batch Number
- 1015 Container Composition/Supplier
- 1016 Closure Composition/Supplier
- 1017 Seal/Supplier
- 1018 Packager/Site/Date
- 1019 Sampling Plan
- 1020 Specifications and Test Methods
- 1021 Storage Conditions
- 1022 Length of Study
- 1023 Reporting Period
- 1024 Location of Data in Application
- 1025 Summary of Data
- 1026 Data Analysis
- 1027 Conclusions

1028 ^a Batches used in clinical studies and biostudies (specify).

1029 ^b Batches of different formulations.

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1030

Table 4: (cont.)

1031

Stability Raw Data for Drug Product X, Batch Y

1032	Product Name/Strength	Study Number	Purpose of Study
1033	Batch Number	Batch Size	Date Study Started
1034	Date Manufactured	Manufacturer/Site	Container/Size/Supplier
1035	Date Packaged	Packager/Site	Closure Supplier
1036	Storage Condition	Storage Orientation	Seal Supplier

1037 Drug Substance Manufacturer/Site/Batch Number

1038 Approved/Proposed Expiration Dating Period

1039

Attributes	Method SOP #	Specification (Low/High)	Time (Months)							
			0	3	6	9	12	18	24	etc.
Appearance										
Assay										
Degradation Product A										
Degradation Product B										
Degradation Product C										
etc.										

1040

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1049 **VII. SPECIFIC STABILITY TOPICS**

1050 **A. Mean Kinetic Temperature**

1051 1. Introduction

1052 Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act states that a drug shall be
1053 deemed to be adulterated if the facilities or controls used for holding drugs do not conform to or
1054 are not operated or administered in conformity with good manufacturing practice to assure that
1055 such drugs meet the requirements of the Act as to safety, and have the identity and strength, and
1056 meet the quality and purity characteristics, which they purport or are represented to possess. This
1057 applies to all persons engaged in manufacture and holding, i.e., storage, of drugs.

1058
1059 Current good manufacturing practices (CGMP) regulations applicable to drug manufacturers (21
1060 CFR 211.142) state that written procedures describing the warehousing of drug products shall be
1061 established and followed. These regulations also state that such procedures shall include
1062 instructions for the storage of drug products under appropriate conditions of temperature,
1063 humidity, and light so the identity, strength, quality, and purity of the drug products are not
1064 affected.

1065 The regulation governing state licensing of wholesale prescription drug distributors (21 CFR
1066 205.50 (c)) states that all prescription drugs shall be stored at appropriate temperatures and under
1067 appropriate conditions in accordance with requirements, if any, in the labeling of such drugs, or
1068 with requirements in the current edition of an official compendium, such as the USP/NF. The
1069 regulation also states that if no storage requirements are established for a prescription drug, the
1070 drug may be held at CRT, as defined in an official compendium, to help ensure that its identity,
1071 strength, quality and purity are not adversely affected (21 CFR 205.50 (c)(1)).

1072 Mean kinetic temperature (MKT) ⁴ is defined as the isothermal temperature that corresponds to
1073 the kinetic effects of a time-temperature distribution. The Haynes formula can be used to
1074 calculate the MKT. It is higher than the arithmetic mean temperature and takes into account the
1075 Arrhenius equation from which Haynes derived his formula. Thus, MKT is the single calculated
1076 temperature that simulates the nonisothermal effects of storage temperature variations. This
1077 section of the guidance explains how to calculate MKT. It also recommends a course of action
1078 should a facility containing products that are labeled for CRT storage fail to maintain the drugs at
1079 appropriate temperature conditions as defined in this guidance. Because MKT is intended to
1080 provide guidance on temperature control of drug storage facilities and is not correlated to any
1081 specific lot of drug product in the storage facility, an MKT in excess of 25°C does not, on its
1082 own, infer that CGMPs have been violated.

⁴ J.D. Haynes, "Worldwide Virtual Temperatures for Product Stability Testing", *J. Pharm. Sci.*, Vol. 60, No. 6, 927 (June 1971).

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1083 2. Calculation

1084 There are a variety of ways to approximate a MKT. The FDA recommends that, for
1085 manufacturers, repackagers, and warehouses, all data points obtained be inserted directly into the
1086 MKT equation. A minimum of weekly high and low readings is recommended, and more rigorous
1087 approximations using daily highs and lows or even more frequent temperature readings would be
1088 acceptable. Storage temperatures may be obtained using automated recording devices, chart
1089 recorders, or a high-low thermometer.

1090 The temperature readings (minimum of 104 weekly high and low readings) would be inserted into
1091 the MKT equation to calculate a yearly MKT. The yearly MKT for the preceding twelve months
1092 should be calculated every month. At times when no drugs are stored in a facility, those intervals
1093 should not be used in MKT calculations. The MKT equation is shown below:

1094
$$T_k = \frac{-\Delta H}{R} \div \ln \left(\frac{e^{-\frac{\Delta H}{RT_{1H}}} + e^{-\frac{\Delta H}{RT_{1L}}} + \dots + e^{-\frac{\Delta H}{RT_{nH}}} + e^{-\frac{\Delta H}{RT_{nL}}}}{2n} \right)$$

1095 Where:

- 1096 T_k = the mean kinetic temperature in °K
- 1097 ΔH = the heat of activation, 83.144 kJ•mole⁻¹
- 1098 R = the universal gas constant, 8.3144 x 10⁻³ kJ•mole⁻¹•°K⁻¹
- 1099 T_{1H} = the high temperature in °K during the 1st week
- 1100 T_{1L} = the low temperature in °K during the 1st week
- 1101 T_{nH} = the high temperature in °K during the nth week
- 1102 T_{nL} = the low temperature in °K during the nth week
- 1103 n = the total number of weeks (i.e. 52)
- 1104 T = absolute temperature in °K
- 1105 °K = °C (Celsius) + 273.2
- 1106 °K = [(°F (Fahrenheit) -32)•0.555] + 273.2

1107 Note that 83.144 kJoules/mol is an average value based upon many common organic reactions.
1108 Since $\Delta H/R = 10,000^\circ\text{K}$, the above equation can be simplified as:

1110
$$T_k = \frac{-10,000}{\ln \left(\frac{e^{-\frac{10,000}{T_{1H}}} + e^{-\frac{10,000}{T_{1L}}} + \dots + e^{-\frac{10,000}{T_{nH}}} + e^{-\frac{10,000}{T_{nL}}}}{2n} \right)}$$

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1112 3. Application

1113 Any time the yearly MKT of a facility approaches 25°C, the occurrence should be documented,
1114 the cause for such an occurrence should be investigated, and corrective actions should be taken to
1115 ensure that the facility is maintained within the established conditions for drug product storage.
1116 FDA recognizes that, when the yearly MKT of a facility begins to exceed 25°C, it may not
1117 necessarily have an impact on products that have been stored for less than one year at the time,
1118 but should be a warning that the facility itself may not be under adequate control.

1119 In addition, whenever the recorded temperature (as opposed to the calculated MKT) exceeds the
1120 allowable excursions of 15-30°C in a facility that contains drugs labeled for storage at CRT, the
1121 occurrence should be documented. The cause for such an occurrence should be investigated, and
1122 corrective actions taken to ensure that the facility is maintained within the established conditions
1123 for drug product storage. The FDA recognizes that brief spikes outside of 15-30°C may, in fact,
1124 be expected from time to time in the real world and may not necessarily have an impact on
1125 product quality. However, depending on the duration and extent of such an exposure and the
1126 dosage form, it may be necessary to determine if the product quality has been adversely affected.

1127 **B. Container/Closure**

1128 Stability data should be developed for the drug product in each type of immediate container and
1129 closure proposed for marketing, promotion, or bulk storage. The possibility of interaction
1130 between the drug and the container and closure and the potential introduction of extractables into
1131 the drug product formulations during storage should be assessed during container/closure
1132 qualification studies using sensitive and quantitative procedures. These studies are recommended
1133 even if the container and closure meet compendial suitability tests, such as those outlined in the
1134 USP for plastic containers and elastomeric or plastic closures. A draft guidance is available on
1135 this topic entitled *Submission of Documentation in Drug Applications for Container Closure*
1136 *Systems Used for the Packaging of Human Drugs and Biologics* (June 1997).

1137 1. Container and Closure Size

1138 Stability data for a given strength may be bracketed by obtaining data for the smallest and the
1139 largest container and closure to be commercially marketed, provided that the intermediate
1140 container and closure is of comparable composition and design (Section VII.G.).

1141 Physician and/or promotional samples that are in different containers and closures or sizes from
1142 the marketed package should be included in the stability studies. Samples in similar container
1143 closure systems may be included in bracketing or matrixing studies (Section VII.H.).
1144 For solid oral dosage forms packaged in large containers (i.e., those not intended for direct
1145 distribution to the patient) full stability studies should be performed if further packaging by health
1146 institutions or contract packagers is anticipated. Samples for stability testing at different time
1147 points may be taken from the same container. Stability data also may be necessary when the
1148 finished dosage form is stored in interim bulk containers prior to filling into the marketed package.
1149 If the dosage form is stored in bulk containers for over 30 days, real-time stability data under

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1150 specified storage conditions should be generated to demonstrate comparable stability to the
1151 dosage form in the marketed package. Interim storage of the dosage form in bulk containers
1152 should generally not exceed six months. The computation of the expiration dating period of the
1153 final marketed product should begin within 30 days of the date of production (see Glossary) of the
1154 dosage form, as defined in the section on Computation of Expiration Dating Period (Section
1155 VII.F.1.), irrespective of the packaging date. If the dosage form is shipped in bulk containers
1156 prior to final packaging, a simulated study may be important to demonstrate that adverse shipping
1157 and/or climatic conditions do not affect its stability.

1158 **2. Container Orientations**

1159 Solutions (i.e., oral, SVPs, LVPs, oral and nasal inhalations, and topical preparations), dispersed
1160 systems (oral, MDIs, injectables), and semi-solid drug products (topical, ophthalmics, and otics)
1161 should be stored in both the upright and either inverted or on-the-side positions until contact with
1162 the container/closure system has been shown not to impact on drug product quality. The
1163 comparison between upright and inverted or on-the-side position is important to determine
1164 whether contact of the drug product (or solvent) with the closure results in extraction of chemical
1165 substances from the closure components or adsorption and absorption of product components
1166 into the container/closure. The evaluation should include the set of test parameters that are listed
1167 in Considerations for Specific Dosage Forms (Section VIII.). Upright versus inverted/on-the-side
1168 stability studies should be performed during the preapproval and postapproval verification stages
1169 of the stability program. Once it has been demonstrated that the product in maximum contact
1170 with the primary pack does not have a significantly greater impact on drug product quality than
1171 the upright orientation, stability studies may be continued only in the most stressful orientation,
1172 which is generally the inverted or on-the-side position.

1173 **3. Extractables and Adsorption/Absorption of Drug Product Components**

1174 Specific extractables testing on a drug product is not recommended. Inverted versus upright
1175 stability testing during preapproval and postapproval verification is usually adequate. Extensive
1176 testing for extractables should be performed as part of the qualification of the container/closure
1177 components, labels, adhesives, colorants and ink (see previously cited packaging guidance for
1178 additional information). Such testing should demonstrate that the levels of extractables found
1179 during extraction studies, which are generally performed with various solvents, elevated
1180 temperatures and prolonged extraction times, are at levels determined to be acceptable, and that
1181 those levels will not be approached during the shelf life of the drug product.

1182 Loss of the active drug substance or critical excipients of the drug product by interaction with the
1183 container/closure components or components of the drug delivery device is generally evaluated as
1184 part of the stability protocol. This is usually accomplished by assaying those critical drug product
1185 components, as well as monitoring various critical parameters (e.g., pH, preservative
1186 effectiveness). Excessive loss of a component or change in a parameter will result in the failure of
1187 the drug product to meet applicable specifications.

1188 **C. Microbiological Control and Quality**

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1189 1. Preservatives Effectiveness

1190 Both sterile and nonsterile drug products may contain preservative systems to control bacteria and
1191 fungi that may be inadvertently introduced during manufacturing. Acceptance criteria should be
1192 provided as part of the drug product specifications for the chemical content of preservatives at the
1193 time of product release and/or through the product shelf life.

1194 The minimum acceptable limit for the content of preservatives in a drug product should be
1195 demonstrated as microbiologically effective by performing a microbial challenge assay of the drug
1196 formulated with an amount of preservative less than the minimum amount specified as acceptable.
1197 This approach provides a margin of safety within the limit and a margin of error for the assays.
1198 Additionally, compatibility of the preservative system with the container, closure, formulation and
1199 devices (e.g., pumps, injection pens) should be demonstrated over the contact period. Multiple
1200 use container systems, for example, containers that are used after the closure is replaced with an
1201 applicator or dropper and large bottles containing syrups or suspensions should be tested for the
1202 microbiological effectiveness of the preservatives system following simulated uses, including
1203 breaches of the container system as permitted in the labeling. USP “Antimicrobial
1204 Preservatives-Effectiveness” provides a microbial challenge assay.

1205 For the purpose of approval of drug applications, stability data on pilot-scale batches should
1206 include results from microbial challenge studies performed on the drug product at appropriate
1207 intervals. Generally, microbial challenge studies conducted initially, annually, and at the end of
1208 the expiration dating period are adequate. Chemical assays of preservative content(s) should be
1209 performed at all test points.

1210 For postapproval testing, the first three production batches should be tested with a microbial
1211 challenge assay at the start and the end of the stability period and at one point in the middle of the
1212 stability period if the test period equals or exceeds two years. The first three production batches
1213 should be assayed for the chemical content of the preservatives at all appropriate test points.
1214 Upon demonstration of chemical content commensurate with microbial effectiveness in the first
1215 three production batches, chemical assays may be adequate to demonstrate the maintenance of the
1216 specified concentrations of preservatives for subsequent annual batches placed into stability
1217 testing.

1218 2. Microbiological Limits for Nonsterile Drug Products

1219 Nonsterile drug products that have specified microbial limits for drug product release should be
1220 tested for conformance to the specified limits at appropriate, defined time points during stability
1221 studies. The USP provides microbiological test methods for microbial limits and guidance
1222 concerning microbiological attributes of nonsterile drug products.

1223 3. Sterility Assurance for Sterile Drug Products

1224 The stability studies for sterile drug products should include data from a sterility test of each batch
1225 at the beginning of the test period. Additional testing is recommended to demonstrate

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1226 maintenance of the integrity of the microbial barrier provided by the container and closure system.
1227 These tests should be performed annually and at expiry.

1228 Integrity of the microbial barrier should be assessed using an appropriately sensitive and
1229 adequately validated container and closure integrity test. The sensitivity of this test should be
1230 established and documented to show the amount of leakage necessary to detect a failed barrier in
1231 a container and closure system. The number of samples to be tested should be similar to the
1232 sampling requirement provided in current USP “Sterility Tests” <71>. The samples that pass
1233 container and closure integrity testing may be used for other stability testing for that specific time
1234 point, but should not be returned to storage for future stability testing. Container and closure
1235 integrity tests do not replace the current USP “Sterility Tests” <71> or 21 CFR 610.12 for
1236 product release.

1237 **4. Pyrogens and Bacterial Endotoxins**

1238 Drug products with specified limits for pyrogens or bacterial endotoxins should be tested at the
1239 time of release and at appropriate intervals during the stability period. For most parenteral
1240 products, testing at the beginning and the end of the stability test period may be adequate. Sterile
1241 dosage forms containing dry materials (powder filled or lyophilized products) and solutions
1242 packaged in sealed glass ampoules may need no additional testing beyond the initial time point.
1243 Products containing liquids in glass containers with flexible seals or in plastic containers should be
1244 tested no less than at the beginning and the end of the stability test period. For test procedures
1245 and specifications, refer to the FDA *Guideline on Validation of the Limulus Amoebocyte Lysate*
1246 *Test as an End-Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological*
1247 *Products, and Medical Devices*, the USP “Bacterial Endotoxins Test” <85>, and the USP
1248 “Pyrogen Test” <151>.

1249 **D. Stability Sampling Considerations**

1250 The design of a stability study is intended to establish, based on testing a limited number of
1251 batches of a drug product, an expiration dating period applicable to all future batches of the drug
1252 product manufactured under similar circumstances. This approach assumes that inferences drawn
1253 from this small group of tested batches extend to all future batches. Therefore, tested batches
1254 should be representative in all respects such as formulation, manufacturing site, container and
1255 closure, manufacturing process, source and quality of bulk material of the population of all
1256 production batches and conform with all quality specifications of the drug product.

1257 The design of a stability study should take into consideration the variability of individual dosage
1258 units, of containers within a batch, and of batches to ensure that the resulting data for each dosage
1259 unit or container are truly representative of the batch as a whole and to quantify the variability
1260 from batch to batch. The degree of variability affects the confidence that a future batch would
1261 remain within specifications until its expiration date.

1262 **1. Batch Sampling**

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1263 Batches selected for stability studies should optimally constitute a random sample from the
1264 population of production batches. In practice, the batches tested to establish the expiration dating
1265 period are often made at a pilot plant that may only simulate full-scale production. Future
1266 changes in the production process may thus render the initial stability study conclusions obsolete.

1267 At least three batches, preferably more, should be tested to allow an estimate of batch-to-batch
1268 variability and to test the hypothesis that a single expiration dating period for all batches is
1269 justifiable. Testing of less than three batches does not permit a reliable estimate of batch-to-batch
1270 variability unless a significant body of information is available on the dosage form and/or drug
1271 product. Although data from more batches will result in a more precise estimate, practical
1272 considerations prevent collection of extensive amounts of data. When a significant body of
1273 information is not available, testing at least three batches represents a compromise between
1274 statistical and practical considerations.

1275 2. Container, Closure, and Drug Product Sampling

1276 Selection of containers, such as bottles, packages, and vials, from the batch chosen for inclusion in
1277 the stability study should ensure that the samples represent the batch as a whole. This can be
1278 accomplished by taking a random sample of containers from the finished batch, by using a
1279 stratification plan whereby at a random starting point every n th container is taken from the filling
1280 or packaging line (n is chosen such that the sample is spread over the whole batch), or by some
1281 other plan designed to ensure an unbiased selection.

1282 Generally, samples to be assayed at a given sampling time should be taken from previously
1283 unopened containers. For this reason, at least as many containers should be sampled as the
1284 number of sampling times in the stability study.

1285 For products packaged in containers intended for dispensing by a pharmacy to multiple patients,
1286 or intended for repackaging or packaged in unit-of-use containers, samples may be taken from
1287 previously opened containers. More than one container should be sampled during the stability
1288 study. The sampling protocol should be submitted in the drug application.

1289 Dosage units should be sampled from a given container randomly, with each dosage unit having
1290 an equal chance of being included in the sample. If the individual units entered the container
1291 randomly, then samples may be taken from units at the opening of the container. However,
1292 because dosage units near the cap of large containers may have different stability properties than
1293 dosage units in other parts of the container, dosage units should be sampled from all parts of the
1294 container. For dosage units sampled in this fashion, the location within the container from which
1295 the samples were taken should be documented and this information included with the test results.

1296 Unless the product is being tested for homogeneity, composites may be assayed instead of
1297 individual units. If more than one container is sampled at a given sampling time, an equal number
1298 of units from each container may be combined into the composite. If composites are used, their
1299 makeup should be described in the stability study report. The same type of composite should be
1300 used throughout the stability study. For example, if 20-tablet composites are tested initially, then

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1301 20-tablet composites should be used throughout. If a larger sample at a given sampling time is
1302 desired, replicated 20-tablet composites should be assayed rather than a single assay of a
1303 composite made from more than 20 tablets. An average of these composite values may be used
1304 for the release assay. However, the individual assay values should be reported as well. Although
1305 other release and stability tests may be performed on these samples (e.g., impurities, preservatives
1306 effectiveness), the results of these tests do not need to be subjected to top/middle/bottom
1307 comparisons.

1308 Semisolid drug products in sizes that are intended for multiple uses should be tested for
1309 homogeneity. Homogeneity testing may be bracketed by container and/or fill size, with testing
1310 done only on the smallest and largest marketed package sizes of each strength. Stability protocols
1311 should provide for increased testing in the event of homogeneity failures, or following a change in
1312 packaging materials or procedures, for example, with a change to a new sealant, or a change in
1313 tube crimping procedures. Where the largest marketed size is more than 20 times the smallest,
1314 homogeneity testing of an intermediate size is recommended.

1315 Semisolid drug products in sizes that are intended for single use need not be tested for
1316 homogeneity.

1317 3. Sampling Time

1318 The sample time points should be chosen so that any degradation can be adequately profiled (i.e.,
1319 at a sufficient frequency to determine with reasonable assurance the nature of the degradation
1320 curve). Usually, the relationship can be adequately represented by a linear, quadratic, or cubic
1321 function on an arithmetic or a logarithmic scale.

1322 Stability testing for long-term studies generally should be performed at three-month intervals
1323 during the first year, six-month intervals during the second, and yearly thereafter. For drug
1324 products predicted to degrade more rapidly, for example, certain radiopharmaceuticals, the
1325 intervals between sampling times should be shortened. Stability testing for accelerated studies
1326 generally should be performed at a minimum of four time points, including the initial sampling
1327 time.

1328 Freezing samples after sampling for the convenience of scheduling analysis is not an acceptable
1329 practice because it may cause delay in finding and responding to out-of-specification test results,
1330 or may adversely affect the stability of a product that does not withstand freezing.

1331 The degradation curve is estimated most precisely, in terms of the width of the confidence limit
1332 about the mean curve (Figure 1, Section VII.E.2.), around the average of the sampling times
1333 included in the study. Therefore, testing an increased number of replicates at the later sampling
1334 times, particularly the latest sampling time, is encouraged because this will increase the average
1335 sampling time toward the desired expiration dating period.

1336 4. Annual Stability Batches

1337 After the expiration dating period has been verified with three production batches, a testing

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1338 program for an approved drug product should be implemented to confirm on-going stability. For
1339 every approved application, at least one batch of every strength in every approved
1340 container/closure system, such as bottles or blisters, should be added to the stability program
1341 annually in all subsequent years. If the manufacturing interval is greater than one year, the next
1342 batch of drug product released should be added to the stability program. Bracketing and
1343 matrixing can be used to optimize testing efficiency.

1344 The recommendations in this section do not apply to compressed medical gases, blood, or blood
1345 products.

1346 **E. Statistical Considerations and Evaluation**

1347 1. Data Analysis and Interpretation for Long-term Studies

1348 A stability protocol should describe not only how the stability study is to be designed and carried
1349 out, but also the statistical method to be used in analyzing the data. This section describes an
1350 acceptable statistical approach to the analysis of stability data and the specific features of the
1351 stability study that are pertinent to the analysis. Generally, an expiration dating or retest period
1352 should be determined based on statistical analysis of observed long-term data. Limited
1353 extrapolation of the real-time data beyond the observed range to extend the expiration dating or
1354 retest period at approval time may be considered if it is supported by the statistical analysis of
1355 real-time data, satisfactory accelerated data, and other nonprimary stability data.

1356 The methods described in this section are used to establish with a high degree of confidence an
1357 expiration dating period during which average drug product attributes such as assay and
1358 degradation products of the batch will remain within specifications. This expiration dating period
1359 should be applicable to all future batches produced by the same manufacturing process for the
1360 drug product.

1361 If an applicant chooses an expiration dating period to ensure that the characteristics of a large
1362 proportion of the individual dosage units are within specifications, different statistical methods
1363 than those proposed below should be considered.⁵ In this setting, testing of individual units,
1364 rather than composites, may be important.

1365 Applicants wishing to use a statistical procedure other than those discussed in this guidance
1366 should consult with the chemistry review team prior to the initiation of the stability study and data
1367 analysis.

1368 2. Expiration Dating Period for an Individual Batch

1369 The time during which a batch may be expected to remain within specifications depends not only
1370 on the rate of physical, chemical or microbiological changes, but also on the initial average value

⁵ R.G. Easterling, J. Am. Stat. Assoc., "Discrimination Intervals for Percentiles in Regression", 64, 1031-41, 1969.

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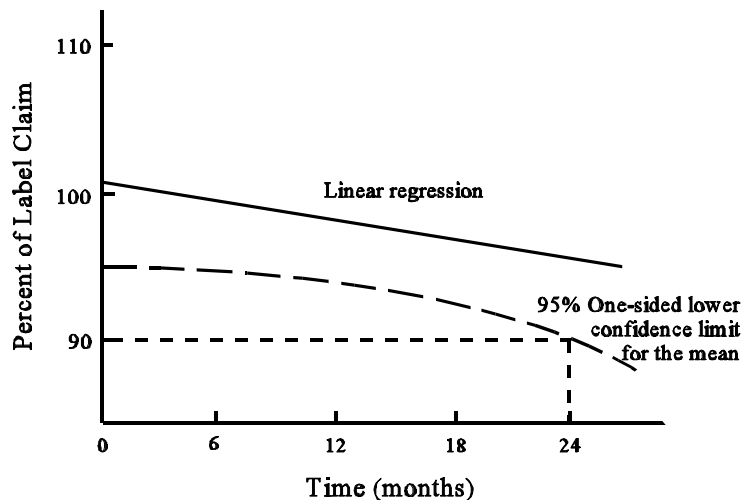
1371 for the batch. Thus, information on the initial value for the batch is relevant to the determination
1372 of the allowable expiration dating period and should be included in the stability study report.
1373 Percentage of label claim, not percentage of initial average value, is the variable of interest.

1374 The expiration dating period for an individual batch is based on the observed pattern of change in
1375 the quantitative attributes (e.g., assay, degradation products) under study and the precision by
1376 which it is estimated.

1377 An acceptable approach for analyzing an attribute that is expected to decrease with time is to
1378 determine the time at which the 95 percent one-sided lower confidence limit, also known as the 95
1379 percent lower confidence bound, for the estimated curve intersects the acceptable lower
1380 specification limit. In the example shown in Figure 1 where the estimated curve is assumed to be
1381 linear based on 24 months of real time data and the lower specification limit is assumed to be 90
1382 percent of label claim, an expiration dating period of 24 months could be granted. When
1383 analyzing an attribute that is expected to increase with time, the 95 percent one-sided upper
1384 confidence limit for the mean is recommended.

1385 When analyzing an attribute with both an upper and a lower specification limit, special cases may
1386 lead to application of a two-sided 95 percent confidence limit. For example, although chemical
1387 degradation of the active ingredient in a solution product would cause a decrease in the assayed

Figure 1: Statistical Analysis of Long-Term Stability Data



1388 concentration, evaporation of the solvent in the product (through the container/closure) would
1389 result in an increase in the concentration. Because both possibilities should be taken into account,
1390 two-sided confidence limits would be appropriate. If both mechanisms were acting, the
1391 concentration might decrease initially and then increase. In this case, the degradation pattern
1392 would not be linear, and more complicated statistical approaches should be considered.

1393 If the approach presented in this section is used, average parameters such as assay and

1394 degradation products of the dosage units in the batch can be expected to remain within
1395 specifications to the end of the expiration dating period at a confidence level of 95 percent. The
1396 expiration dating period should not be determined using the point at which the fitted least-squares
1397 line intersects the appropriate specification limit. This approach is as likely to overestimate the
1398 expiration dating period as to underestimate it, in which case the batch average can be expected to
1399 remain within specifications at expiration if the fitted least-squares line is used with a confidence
1400 level of only 50 percent.

1401 The statistical assumptions underlying the procedures described above, such as the assumption
1402 that the variability of the individual units from the batch average remains constant over the several
1403 sampling times, are well known and have been discussed in numerous statistical texts. The above
1404 procedures will remain valid even when these assumptions are violated to some degree. If severe
1405 violation of the assumptions in the data is noted, an alternate approach may be necessary to
1406 accomplish the objective of determining an expiration dating period with a high degree of
1407 confidence.

1408 3. Expiration Dating Period for All Batches

1409 If batch-to-batch variability is small, that is, the relationship between the parameter of interest
1410 such as assay or degradation products and time is essentially the same from batch to batch,
1411 stability data should be combined into one overall estimate. Combining the data should be
1412 supported by preliminary testing of batch similarity.⁶ The similarity of the estimated curves
1413 among the batches tested should be assessed by applying statistical tests of the equality of slopes
1414 and of zero time intercepts. The level of significance of the tests, expressed in the p-value, should
1415 be chosen so that the decision to combine the data is made only if there is strong evidence in favor
1416 of combining. A p-value of 0.25 for preliminary statistical tests has been recommended.⁷ If the
1417 tests for equality of slopes and for equality of intercepts do not result in rejection at a level of
1418 significance of 0.25, the data from the batches could be pooled. If these tests resulted in p-values
1419 less than 0.25, a judgment should be made as to whether pooling could be permitted. The
1420 appropriate FDA chemistry review team should be consulted regarding this determination.

1421 If the preliminary statistical test rejects the hypothesis of batch similarity because of unequal initial
1422 intercept values, it may still be possible to establish that the lines are parallel (i.e., that the slopes
1423 are equal). If so, the data may be combined for the purpose of estimating the common slope. The
1424 individual expiration dating period for each batch in the stability study may then be determined by
1425 considering the initial values and the common slope using appropriate statistical methodology. If
1426 data from several batches are combined, as many batches as feasible should be combined because
1427 confidence limits about the estimated curve will become narrower as the number of batches
1428 increases, usually resulting in a longer expiration dating period. If it is inappropriate to combine

⁶K.K. Lin, T-Y.D. Lin, and R.E. Kelley, "Stability of Drugs: Room Temperature Tests", in *Statistics in the Pharmaceutical Industry*, ed. C.R. Buncher and J-Y. Tsay, pp. 419-444, Marcel Dekker, Inc.: New York, 1994.

⁷T. A. Bancroft, "Analysis and Inference for Incompletely Specified Models Involving the Use of Preliminary Test(s) of Significance," *Biometrics*, 20(3), 427-442, 1964.

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1429 data from several batches, the overall expiration dating period will depend on the minimum time a
1430 batch may be expected to remain within acceptable limits.

1431 4. Precautions in Extrapolation Beyond Actual Data

1432 The statistical methods for determining an expiration dating period beyond the observed range of
1433 time points are the same as for determining an expiration dating period within the observed range.
1434 The a priori correctness of the assumed pattern of change as a function of time is crucial in the
1435 case of extrapolation beyond the observed range. When estimating a line or curve of change
1436 within the observed range of data, the data themselves provide a check on the correctness of the
1437 assumed relationship, and statistical methods may be applied to test the goodness of fit of the data
1438 to the line or curve. No such internal check is available beyond the range of observed data. For
1439 example, if it has been assumed that the relationship between log assay and time is a straight line
1440 when, in fact, it is a curve, it may be that within the range of the observed data, the true curve is
1441 close enough to a straight line that no serious error is made by approximating the relationship as a
1442 straight line. However, beyond the observed data points, the true curve may diverge from a
1443 straight line enough to have a significant effect on the estimated expiration dating period.

1444 For extrapolation beyond the observed range to be valid, the assumed change must continue to
1445 apply through the estimated expiration dating period. Thus, an expiration dating period granted
1446 on the basis of extrapolation should always be verified by actual stability data as soon as these
1447 data become available.

1448 **F. Expiration Dating Period/Retest Period**

1449 1. Computation of Expiration Date

1450 The computation of the expiration dating period of the drug product should begin no later than
1451 the time of quality control release of that batch, and the date of release should generally not
1452 exceed 30 days from the production date, regardless of the packaging date. The data generated in
1453 support of the assigned expiration dating period should be from long-term studies under the
1454 storage conditions recommended in the labeling. If the expiration date includes only a month and
1455 year, the product should meet specifications through the last day of the month.

1456 In general, proper statistical analysis of long-term stability data collected, as recommended in
1457 Section VII.E. and exemplified in Figure 1, should support at least a one-year expiration dating
1458 period. Exceptions do exist, for example, with short half-life radioactive drug products.

1459 If the production batch contains reprocessed material, the expiration dating period should be
1460 computed from the date of manufacture of the oldest reprocessed material used.

1461 a. Extension of Expiration Dating Period

1462 An extension of the expiration dating period based on full long-term stability data obtained from
1463 at least three production batches in accordance with a protocol approved in the application may
1464 be described in an annual report (21 CFR 314.70(d)(5)). The expiration dating period may be

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1465 extended in an annual report only if the criteria set forth in the approved stability protocol are met
1466 in obtaining and analyzing data, including statistical analysis, if appropriate.

1467 Alternatively, if the stability study on at least three pilot-scale batches is continued after the
1468 NDA/BLA approval, it is feasible to extend the tentative expiration dating period based on full
1469 long-term data obtained from these batches in accordance with the approved protocol, including
1470 statistical analysis if appropriate, through a prior approval supplement. However, the expiration
1471 dating period thus derived remains tentative until confirmed with full long-term data from at least
1472 three production batches.

1473 Unless a new stability protocol has been adopted via a prior approval supplement before the
1474 change is made, stability protocols included in drug applications prior to the 1985 revisions to the
1475 NDA regulations (50 FR 7452) may not support the extension of expiration dating periods
1476 through annual reports. If the data are obtained under a *new* or *revised* stability protocol, a prior
1477 approval supplement under 21 CFR 314.70(b) or (g) or 21 CFR 601.12 should be submitted to
1478 extend the expiration dating period.

1479 b. Shortening of Expiration Dating Period

1480 When warranted, a previously approved expiration dating period may be shortened via a changes-
1481 being-effected supplement (21 CFR 314.70(c)(1) or 21 CFR 601.12). The supplemental
1482 application should provide pertinent information and the data that led to the shortening of the
1483 expiration dating period. The expiration dating period should be shortened to the nearest
1484 available real-time long-term test point where the product meets acceptance criteria. The
1485 expiration dating period thus derived should be applied to all subsequent production batches and
1486 may not be extended until the cause for the shortening is fully investigated, the problem is
1487 resolved, and satisfactory stability data become available on at least three new production batches
1488 to cover the desired expiration dating period and are submitted in a changes-being-effected
1489 supplement.

1490 2. Retest Period for Drug Substance

1491 A retest period for a drug substance may be established based on the available data from
1492 long-term stability studies and, as such, can be longer than 24 months if supported by data. A
1493 retest date should be placed on the storage container and on the shipping container for a bulk
1494 drug substance. A drug substance batch may be used without retest during an approved retest
1495 period. However, beyond the approved retest period, any remaining portion of the batch should
1496 be retested immediately before use. Retest of different portions of the same batch for use at
1497 different times as needed is acceptable, provided that the batch has been stored under the defined
1498 conditions, the test methods are validated and stability-indicating, and all stability-related
1499 attributes are tested and test results are satisfactory.

1500 Satisfactory retest results on a drug substance batch after the retest date do not mean that the
1501 retest period can be extended for that batch or any other batch. The purpose of retest is to qualify
1502 a specific batch of a drug substance for use in the manufacture of a drug product, rather than to

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1503 recertify the drug substance with a new retest date. To extend the retest period, full long-term
1504 data from a formal stability study on three production batches using a protocol approved in an
1505 application or found acceptable in a DMF should be provided.

1506 Similar to the extension of an expiration dating period for a drug product, a retest period for a
1507 drug substance may be extended beyond what was approved in the original application. This can
1508 be achieved through an annual report based on full long-term stability data (i.e., covering the
1509 desired retest period on three production batches using an approved stability protocol).

1510 In a case where testing reveals a limited shelf-life for a drug substance, it may be inappropriate to
1511 use a retest date. An expiration dating period, rather than a retest period, should be established
1512 for a drug substance with a limited shelf-life (e.g., some antibiotics, biological substances).

1513 **3. Holding Times for Drug Product Intermediates**

1514 Intermediates such as blends, triturates, cores, extended-release beads or pellets may be held for
1515 up to 30 days from their date of production without being retested prior to use. An intermediate
1516 that is held for longer than 30 days should be monitored for stability under controlled, long-term
1517 storage conditions for the length of the holding period. In addition, the first production batch of
1518 the finished drug product manufactured with such an intermediate should be monitored on
1519 long-term stability. When previous testing of an intermediate or the related drug product batches
1520 suggests that an intermediate may not be stable for 30 days, the holding time should be kept to a
1521 minimum and qualified by appropriate stability testing.

1522 The frequency of testing of an intermediate on stability is related to the length of the holding time.
1523 Where practical, testing should be done at a minimum of three time points after the initial testing
1524 of an intermediate. At a minimum, all critical parameters should be evaluated at release of an
1525 intermediate and immediately prior to its use in the manufacture of the finished drug product.

1526 In the event that the holding time for an intermediate has not been qualified by appropriate
1527 stability evaluations, the expiration date assigned to the related finished drug product batch should
1528 be computed from the quality control release date of the intermediate if this date does not exceed
1529 30 days from the date of production of the intermediate. If the holding time has been qualified by
1530 appropriate stability studies, the expiration date assigned to the related finished drug product can
1531 be computed from its quality control release date if this release date does not exceed 30 days from
1532 the date that the intermediate is introduced into the manufacture of the finished drug product.

1533 **G. Bracketing**

1534 **1. General**

1535 The use of reduced stability testing, such as a bracketing design, may be a suitable alternative to a
1536 full testing program where the drug is available in multiple sizes or strengths. This section
1537 discusses the types of products and submissions to which a bracketing design is applicable and the
1538 types of factors that can be bracketed. Applicants are advised to consult with the FDA when

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1539 questions arise.

1540 2. Applicability

1541 The factors that may be bracketed in a stability study are outlined in ICH Q1A and described in
1542 further detail below. The types of drug products and the types of submissions to which
1543 bracketing design can be applied are also discussed.

1544 a. Types of drug product

1545 Bracketing design is applicable to most types of drug products, including immediate- and
1546 modified-release oral solids, liquids, semi-solids, injectables. Certain types of drug products, such
1547 as metered-dosed inhalers (MDIs), dry powder inhalers (DPIs) and transdermal delivery systems
1548 (TDSs), may not be amenable to, or may need additional justification for, bracketing design.

1549 b. Factors

1550 Where a range of container/fill sizes for a drug product of the same strength is to be evaluated,
1551 bracketing design may be applicable if the material and composition of the container and the type
1552 of closure are the same throughout the range. In a case where either the container size or fill size
1553 varies while the other remains the same, bracketing design may be applicable without justification.
1554 In a case where both container size and fill size vary, bracketing design is applicable if appropriate
1555 justification is provided. Such justification should demonstrate that the various aspects (surface
1556 area/volume ratio, dead-space/volume ratio, container wall thickness, closure geometry) of the
1557 intermediate sizes will be adequately bracketed by the extreme sizes selected.

1558 Where a range of dosage strengths for a drug product in the same container/closure (with
1559 identical material and size) is to be tested, bracketing design may be applicable if the formulation
1560 is identical or very closely related in components/composition. Examples for the former include a
1561 tablet range made with different compression weights of a common granulation, or a capsule
1562 range made by filling different plug fill weights of the same composition into different size capsule
1563 shells. The phrase *very closely related formulation* means a range of strengths with a similar, but
1564 not identical, basic composition such that the ratio of active ingredient to excipients remains
1565 relatively constant throughout the range (e.g., addition or deletion of a colorant or flavoring).

1566 In the case where the amount of active ingredient changes while the amount of each excipient or
1567 the total weight of the dosage unit remains constant, bracketing may not be applicable unless
1568 justified. Such justification may include a demonstration of comparable stability profile among the
1569 different strengths based on data obtained from clinical/development batches, primary stability
1570 batches, and/or production batches in support of primary stability batches, commitment batches,
1571 and/or annual batches and batches for postapproval changes, respectively. With this approach,
1572 the formulations should be identical or very closely related, and the container/closure system
1573 should be the same between the supportive batches and the batches for which the bracketing

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1574 design is intended.

1575 If the formulation is significantly different among the different strengths (e.g., addition or deletion
1576 of an excipient, except colorant or flavoring), bracketing is generally not applicable.

1577 Due to the complexity in product formulation, applicants are advised to consult the appropriate
1578 chemistry review team in advance when questions arise in the above situations or where
1579 justification is needed for bracketing design.

1580 In the case where the strength and the container and/or fill size of a drug product both vary,
1581 bracketing design may be applicable if justified.

1582 c. Types of submissions

1583 A bracketing design may be used for primary stability batches in an original application,
1584 postapproval commitment batches, annual batches, or batches intended to support supplemental
1585 changes. Bracketing design should not be applied to clinical batches during the IND stages when
1586 the product is still under development. Where additional justification is needed for applying a
1587 bracketing design, product stability should be demonstrated using supportive data obtained from
1588 clinical/development or NDA batches, commitment batches, or production batches. Before a
1589 bracketing protocol is applied to primary stability batches to support an application, the protocol
1590 should be endorsed by Agency chemistry staff via an IND amendment, an end-of-phase 2 meeting,
1591 or prior to submission of an ANDA. Bracketing protocols to be applied to postapproval
1592 commitment batches and annual batches, if proposed, will be approved as part of the original
1593 application.

1594 A bracketing design that is not contained in the approved protocol in the application is subject to
1595 supplemental approval (21 CFR 314.70(b)(2)(ix)) (601.12). If the new bracketing design is used
1596 to generate stability data to support two different chemistry, manufacturing or controls changes,
1597 the two proposed changes could be combined into one prior-approval supplement even though
1598 the latter may otherwise qualify for a changes-being-effected supplement or annual report under
1599 314.70 (c) or (d) or 601.12, or relevant SUPAC guidances. Alternatively, the applicant may
1600 consult the appropriate Agency review staff through general correspondence regarding the
1601 acceptability of the new bracketing design prior to the initiation of the stability studies, and
1602 subsequently submit the data to support the proposed change through the appropriate filing
1603 mechanism.

1604 3. Design

1605 A bracketing protocol should always include the extremes of the intended commercial sizes and/or
1606 strengths. Physician samples or bulk pharmacy packs intended to be repackaged should be
1607 excluded from the bracketing protocol for commercial sizes, but could be studied under their own
1608 bracketing protocols, if applicable. Where a large number, for example four or more, of

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1609 sizes/strengths is involved, the inclusion of the one batch each of the intermediates or three
 1610 batches of the middle size/strength in the bracketing design is recommended. Where the ultimate
 1611 commercial sizes/strengths differ from those bracketed in the original application, a commitment
 1612 should be made to place the first production batches of the appropriate extremes on the stability
 1613 study postapproval. Such differences should, however, be justified. Where additional justification
 1614 for the bracketing design is needed in the original application, one or more of the first production
 1615 batches of the intermediate(s) should be placed on the postapproval long-term stability study.

1616 An example of bracketing design is presented in Table 5, where both strengths and container/fill
 1617 sizes are bracketed in one protocol and “X” denotes the combination of strength and container/fill
 1618 size to be placed on stability study. In this hypothetical situation, the capsule dosage form is
 1619 available in three different strengths made from a common granulation and packaged in three
 1620 different sizes of HDPE bottles with different fills: 30 counts, C1; 100 counts, C2; and 200
 1621 counts, C3. The surface area/volume ratio, dead space/volume ratio, container wall thickness,
 1622 and closure performance characteristics are assumed to be proportional among the three
 1623 container/fill sizes for each strength of the capsules.

1624 **Table 5: Bracketing Example**

Batch	1									2									3								
Strength	100 mg			200 mg			300 mg			100 mg			200 mg			300 mg			100 mg			200 mg			300 mg		
Container/ Closure	C1	C2	C3	C1	C2	C3	C1	C2	C3	C1	C2	C3	C1	C2	C3	C1	C2	C3	C1	C2	C3	C1	C2	C3	C1	C2	C3
Sample on Stability	X		X				X	X	X	X						X	X	X	X						X		X

1631 4. Data evaluation

1632 The stability data obtained under a bracketing protocol should be subjected to the same type of
 1633 statistical analysis described in Section VII.E. The same principle and procedure on poolability
 1634 should be applied (i.e., testing data from different batches for similarity before combining them
 1635 into one overall estimate). If the statistical assessments of the extremes are found to be dissimilar,
 1636 the intermediate sizes/strengths should be considered to be no more stable than the least stable

1637 extreme.⁸

1638 **H. Matrixing**

1639 1. General

1640 The use of reduced stability testing, such as a matrixing design, may be a suitable alternative to a
1641 full testing program where multiple factors involved in the product are being evaluated. The
1642 principle behind matrixing is described in ICH Q1A. This section provides further guidance on
1643 when it is appropriate to use matrixing and how to design such a study. Consultation with FDA is
1644 encouraged before the design is implemented.

1645 2. Applicability

1646 The types of drug products and the types of submissions to which matrixing design can be applied
1647 are the same as described for bracketing above. The factors that can be matrixed with or without
1648 justification and those that should not be matrixed are discussed below. Additionally, data
1649 variability and product stability, as demonstrated through previous supportive batches, should be
1650 considered when determining if matrixing can be applied to the batches of interest.

1651 a. Types of drug product

1652 Matrixing design is applicable to most types of drug products, including immediate- and modified-
1653 release oral solids, liquids, semisolids, injectables. Certain types of drug products such as MDIs,
1654 DPIs, and TDSs may not be amenable to, or may need additional justification for, matrixing
1655 design.

1656 b. Factors

1657 Some of the factors that can be matrixed include batches, strengths with identical formulation,
1658 container sizes, fill sizes, and intermediate time points. With justification, additional factors that
1659 can be matrixed include strengths with closely related formulation, container and closure
1660 suppliers, container and closure systems, orientations of container during storage, drug substance
1661 manufacturing sites, and drug product manufacturing sites. For example, to justify matrixing
1662 across HDPE bottles and blister packs, a tablet dosage form could be shown not to be sensitive to
1663 moisture, oxygen, or light (through stressed studies, including open-dish experiments) and that it
1664 is so stable that the protective nature of the container/closure system made little or no difference
1665 in the product stability (through supportive data). Alternatively, it could be demonstrated, if

⁸ For additional information on bracketing studies, see W.R. Fairweather, T.-Y. D. Lin, and R. Kelly, "Regulatory, Design, and Analysis Aspects of Complex Stability Studies," *J. Pharm. Sci.*, **84**, 1322-1326, 1995.

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1666 appropriate, that there is no difference in the protective nature between the two distinctively
1667 different container/closure systems. The justification is needed to ensure that the matrixing
1668 protocol would lead to a successful prediction of the expiration dating period when two otherwise
1669 different container/closure systems are studied together.

1670 Factors that should not be matrixed include initial and final time points, attributes (test
1671 parameters), dosage forms, strengths with different formulations (i.e., different excipients or
1672 different active/excipient ratios, and storage conditions).

1673 c. Data variability and Product Stability

1674 The applicability of matrixing design to primary stability batches depends on the product stability
1675 and data variability demonstrated through clinical or developmental batches. Data variability
1676 refers to the variability of supportive stability data within a given factor (i.e., batch-to-batch,
1677 strength-to-strength, size-to-size) and across different factors (e.g., batch vs strength, strength vs
1678 size). It is assumed that there is very little variability in the analytical methods used in the testing
1679 of stability samples. Matrixing design is applicable if these supportive data indicate that the
1680 product exhibits excellent stability with very small variability. Where the product displays
1681 moderate stability with moderate variability in the supportive data, matrixing design is applicable
1682 with additional justification. Conversely, if supportive data suggest poor product stability with
1683 large variability, matrixing design is not applicable. Similarly, whether or not matrixing design can
1684 be applied to postapproval commitment batches or supplemental changes will depend on the
1685 cumulative stability data on developmental batches, primary batches, and/or production batches,
1686 as appropriate.

1687 Table 6 illustrates the range of situations under which matrixing design is applicable, applicable if
1688 justified, generally not applicable, and not applicable. The table is intended, in a qualitative
1689 manner, to serve as a general guide for sponsors when determining if matrixing design is
1690 appropriate for a drug product with respect to the likelihood that such a design would result in a
1691 successful prediction of the expiration dating period. It does not seek to quantitatively define the
1692 different degrees of product stability or data variability.

1693

Table 6: Applicability of Matrixing Design

1694

Data	Product Stability ^a		
Variability ^b	Excellent	Moderate	Poor
Very Small	Applicable	Applicable	Applicable if justified
Moderate	Applicable	Applicable if justified	Generally not applicable
Large	Applicable if justified	Generally not applicable	Not Applicable

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^a In general, *moderate* and *excellent* stability mean little or no change in product test results for a period of 2-3 years and 4-5 years, respectively, as indicated by supportive data. *Poor stability* means measurable changes in test results within 1 year.

^b Variability in supportive stability data within a given factor or across different factors.

1703

d. Types of submission

1704

Same as Section VII.G.1.c.

1705

3. Design

1706

a. General

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For original applications, a matrixing design should always include the initial and final time points, as well as at least two additional time points through the first 12 months, that is at least three time points including the initial and 12-month time points. This approach is especially important if the original application contains less than full long-term data at the time of submission.

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Although matrixing should not be performed across attributes, different matrixing designs for different attributes may be suitable where different testing frequencies can be justified. Likewise, each storage condition should be treated separately under its own matrixing design, if applicable. Care must be taken to ensure that there are at least three time points, including initial and end points, for each combination of factors under an accelerated condition. If bracketing is justified, the matrixing design should be developed afterward.

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All samples should be placed on stability including those that are not to be tested under the matrixing design. Once the study begins, the protocol should be followed without deviation. The

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1719 only exception is that, if necessary, it is acceptable to revert back to full stability testing during the
1720 study. But once reverted, the full testing should be carried out through expiry.

1721 b. Size of matrixing design

1722 The appropriate size of a matrix is generally related to the number of combinations of factors and
1723 the amount of supportive data available (Table 7). The size of a matrixing design is expressed as
1724 a fraction of the total number of samples to be tested in the corresponding full stability protocol.
1725 For a product available in 3 batches, 3 strengths, and 3 container/fill sizes, the number of
1726 combinations of factors to be tested in a full design is 3x3x3 or 27. Similarly, if there are 3
1727 batches with one strength and no other factors, the number of combinations of factors is
1728 expressed as 3x1. The larger the number of combinations of factors to be tested *and* the greater
1729 the amount of available supportive data, the smaller the size of matrixing design that may be
1730 justified. The phrase *substantial amount of supportive data* means that a sufficient length of
1731 stability data are available on a considerable number of clinical/development batches, primary
1732 stability batches, and/or production batches to justify the use of matrixing design on primary
1733 stability batches, commitment batches, and/or annual batches and batches for postapproval
1734 changes. The formulations used in a matrixing design should be identical or very closely related,
1735 and the container/closure system should be the same between the supportive batches and the
1736 batches for which the matrixing design is intended. The size of matrixing design shown in the
1737 table takes into account all possible combinations of factors and time points. For example, where
1738 there are 3x3x3 combinations of factors and a substantial amount of supportive data are available,
1739 the size of the matrixing design could be as small as one half of that of a full testing protocol.
1740 Thus, *fractional* 1/2 means that only one half of the total number of samples in the corresponding
1741 full protocol will be tested under the matrixing design. Refer to Examples 2 and 3 below for two
1742 designs with an overall size of 5/12 and 1/2, respectively.

1743

Table 7: Size of Matrixing Design^a

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Number of Combinations of Factors ^a	Amount of Supportive Data ^c Available		
	Substantial	Moderate	Little or none
Large (e.g., 3x3x3 or greater)	Fractional (e.g., 1/2)	Fractional (e.g., 5/8)	Full (i.e., no matrixing ^d)
Moderate (e.g., 3x2)	Fractional (e.g., 5/8)	Fractional (e.g., 3/4)	Full (i.e., no matrixing)
Very small (e.g., 3x1)	Fractional (e.g., 3/4)	Full (i.e., no matrixing)	Full (i.e., no matrixing)

^a Expressed as a fraction of the total number of samples to be tested in the corresponding full design.

^b Excluding time points.

^c Cumulative stability data obtained from clinical/development batches, primary stability batches, and/or production batches, as appropriate, to form the basis to support the stability profile of the product.

^d *No matrixing* means that matrixing is not suitable.

1759

c. Statistical Considerations

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The design should be well balanced. An estimate of the probability that stability outcomes from the matrixed study would be the same for a given factor or across different factors should be provided if available.⁹

1763

d. Examples

1764

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Matrixing Example #1. Complete design with five-sevenths' time points (overall size: five-sevenths of full testing protocol)

⁹For additional information on matrixing studies see W.R. Fairweather, T.-Y. D. Lin and R. Kelly, "Regulatory, Design, and Analysis Aspects of Complex Stability Studies," *J. Pharm. Sci.*, 84, 1322-1326, 1995.

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1766 The following example (Table 8) involves a complete design of 3x3x3 combinations of
 1767 factors with five-sevenths' time points for a capsule dosage form available in 3 strengths of a
 1768 common granulation and packaged in 3 container/closure systems and/or sizes: C1, HDPE
 1769 bottle; 30 counts; C2, HDPE bottle, 100 counts; and blister-pack. A 24-month expiration
 1770 dating period is proposed. While stability samples for all 27 combinations of factors will be
 1771 tested, they will be tested only at five-sevenths of the usual time points; thus the overall size
 1772 of design is 5/7 of the corresponding full testing protocol.

1773 **Table 8: Matrixing Example #1**

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Batch	1									2									3									
Strength	100 mg			200 mg			300 mg			100 mg			200 mg			300 mg			100 mg			200 mg			300 mg			
Container/ Closure	C1	C2	C3	C1	C2	C3	C1	C2	C3	C1	C2	C3	C1	C2	C3	C1	C2	C3	C1	C2	C3	C1	C2	C3	C1	C2	C3	
Schedule	T1	T2	T3	T2	T3	T1	T3	T1	T2	T2	T3	T1	T3	T1	T2	T1	T2	T3	T3	T1	T2	T1	T2	T3	T2	T3	T1	
Time Points (mo)	0	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
	3	x					x		x				x		x		x				x		x				x	
	6		x		x				x	x					x		x				x		x		x			
	9	x		x		x	x				x	x	x	x		x		x	x	x		x		x		x	x	
	12		x	x	x	x		x		x	x	x		x		x		x	x	x		x		x	x	x	x	
	18	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	24	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

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1782 Matrixing Example #2. Two-thirds fractional design with five-eighths time points (overall
1783 size: five-twelfths of full testing protocol)

1784 The following example (Table 9) involves a two-thirds fractional design of 3x3x3
1785 combinations of factors with five-eighths time points for a capsule dosage form which is
1786 available in 3 strengths of a common granulation and packaged in 3 container/closure
1787 systems and/or sizes: C1, HDPE bottle; 30 counts; C2, HDPE bottle, 100 counts; and C3,
1788 HDPE bottle, 200 counts. A 36-month expiration dating period is proposed. The overall
1789 size of this design can be referred to as 2/3 (of 27 combinations of factors) x 5/8 (of 8 time
1790 points), or 5/12 (of 216 samples in a full testing protocol).

1791 **Table 9: Matrixing Example #2**

Batch		1									2									3											
Strength		100 mg			200 mg			300 mg			100 mg			200 mg			300 mg			100 mg			200 mg			300 mg					
Container/ Closure		C1	C2	C3	C1	C2	C3	C1	C2	C3	C1	C2	C3	C1	C2	C3	C1	C2	C3	C1	C2	C3	C1	C2	C3	C1	C2	C3	C1	C2	C3
Schedule		T1	T2		T2		T1		T1	T2	T2		T1		T1	T2	T1	T2					T1	T2	T1	T2			T2		T1
Time Points (mo)	0	x	x		x		x		x	x	x		x		x	x	x					x	x	x	x	x			x		x
	3	x				x			x				x		x							x		x							x
	6		x		x					x	x				x		x						x		x		x		x		
	9	x				x			x				x		x							x		x							x
	12		x		x					x	x				x		x						x		x		x		x		
	18	x				x			x				x		x							x		x							x
	24		x		x					x	x				x		x						x		x		x		x		
	36	x	x		x		x		x	x	x		x		x	x	x					x	x	x	x	x	x	x		x	x

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1800 Matrixing Example #3. Bracketing design and three-fourths Matrix (overall size: one-half
1801 of full testing protocol)

1802 The following example (Table 10) illustrates how bracketing (of one factor) and matrixing
1803 (with three-fourths time points) can be combined in one protocol. The description of the
1804 drug product is as shown in Example 2. The overall size of this design is 2/3 X 3/4, or 1/2 of
1805 that of a full testing protocol.

1806 **Table 10: Matrixing Example #3**

Batch		1									2									3								
Strength		100 mg			200 mg			300 mg			100 mg			200 mg			300 mg			100 mg			200 mg			300 mg		
Container/ Closure		C1	C2	C3	C1	C2	C3	C1	C2	C3	C1	C2	C3	C1	C2	C3	C1	C2	C3	C1	C2	C ₃	C1	C2	C3	C1	C2	C3
Schedule		T1	T2	T3				T3	T1	T2	T2	T3	T1				T1	T2	T3	T3	T1	T2				T2	T3	T1
Time Points (mo)	0	x	x	x				x	x	x	x	x	x				x	x	x	x	x	x				x	x	x
	3	x	x						x	x	x		x				x	x			x	x				x		x
	6		x	x				x		x	x	x					x	x	x		x				x	x		
	9	x		x				x	x			x	x				x		x	x	x					x	x	
	12	x	x	x				x	x	x	x	x	x				x	x	x	x	x	x				x	x	x
	18	x							x				x				x				x						x	
	24		x	x				x		x	x	x					x	x	x		x				x	x		
36	x	x	x				x	x	x	x	x	x				x	x	x	x	x	x				x	x	x	

1815

1816 4. Data Evaluation

1817 The stability data obtained under a matrixing protocol should be subjected to the same type
1818 of statistical analysis with the same vigor and for the same aspects as outlined in Section
1819 VII.E. The same principle and procedure on poolability (i.e., testing data from different
1820 batches for similarity before combining them into one overall estimate, as described in
1821 Section VII.E.1) should be applied.

1822

1823 **I. Site-Specific Stability Data For Drug and Biologic Applications**

1824 1. Purpose

1825 At the time of NDA submission, at least 12 months of long-term data and 6 months of
1826 accelerated data should be available on three batches of the drug substance (all of which
1827 should be at least pilot scale) and three batches of the drug product (two of which should be
1828 at least pilot scale); reference is made to the drug substance and drug product sections of the
1829 ICH Q1A Guidance and to Sections II.A and II.B. of this guidance, respectively. Because
1830 the ICH Guidance did not address where the stability batches should be made, this section
1831 provides recommendations on site-specific stability data: the number and size of drug
1832 substance and drug product stability batches made at the intended manufacturing-scale
1833 production sites and the length of stability data on these batches, for an original NDA,
1834 ANDA, BLA or PLA application. Applicants are advised to consult with the respective
1835 chemistry review team when questions arise.

1836 2. Original NDAs, BLAs, or PLAs

1837 In principle, primary stability batches should be made at the intended commercial site. If the
1838 primary stability batches are not made at the intended commercial site, stability data from
1839 the drug substance/product batches manufactured at that site (i.e., site-specific batches)
1840 should be included in the original submission to demonstrate that the product made at each
1841 site is equivalent. If at the time of application submission, there are 12 months of long-term
1842 data and 6 months of accelerated data on three primary stability batches made at other than
1843 the intended commercial site, a reduced number of site-specific batches with shorter
1844 duration of data than the primary batches may be acceptable. In addition, these site-specific
1845 batches may be of pilot scale.

1846 A drug substance should be adequately characterized (i.e., results of chemical, physical,
1847 and, when applicable, biological testing). Material produced at different sites should be of
1848 comparable quality. In general, three to six months of stability data on one to three site-
1849 specific drug substance batches, depending on the availability of sufficient primary stability
1850 data from another site, should be provided at the time of application submission. Table 11
1851 depicts the site-specific stability data recommended for the drug substance in an original
1852 application.

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Table 11: Site-Specific Stability Data for a Drug Substance in an Original Application

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Scenario ^a	Site-Specific Stability Data Recommended at Time of Submission ^b	Stability Commitment ^c
Sufficient primary stability data are available for the drug substance	3 months of accelerated (from a 6-month study) and long-term data on 1 site-specific batch.	First 3 drug substance production batches on long-term and accelerated stability studies.
Sufficient primary stability data are not available for the drug substance	3 months of accelerated (from a 6-month study) and long-term data on 3 site-specific batches.	First 3 drug substance production batches on long-term and accelerated stability studies.

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^a The phrase *sufficient primary stability data* means that, at the time of submission, there are 6 months of accelerated data and at least 12 months of long-term data on three primary stability batches made at a different pilot or production site from the intended site.

1865
1866

^b Additional long-term stability data and, if applicable, accelerated data, should be submitted for review as soon as they become available prior to the approval.

1867
1868
1869

^c A commitment should be provided in the application to place the first three production batches at each site on long-term and accelerated stability studies and annual batches thereafter on long-term studies using the approved protocol and to report the resulting data in annual reports.

1870
1871
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The complexity of the drug product dosage form is a critical factor in determining the number of site-specific batches for an original application. The quality and/or stability of a simple dosage form is less likely to vary due to a different manufacturing site than that of a complex dosage form. Three site-specific batches are needed for a complex dosage form to provide an independent and statistically meaningful stability profile for the product made at that site. One site-specific batch may be sufficient to verify the stability profile of a simple dosage form. Table 12, below, illustrates the site-specific stability data recommended for drug products in an original application:

Table 12: Site-Specific Stability Data for a Drug Product in an Original NDA, BLA, or PLA

Scenario ^a	Site-Specific Stability Data Recommended at Time of Submission ^b	Stability Commitment ^c
Simple dosage form where sufficient primary stability data are available	3 months of accelerated (from a 6-month study) and long-term data on 1 site-specific batch.	First 3 production batches on long-term and accelerated stability studies.
Complex dosage form where sufficient primary stability data are available	3 months of accelerated (from a 6-month study) and long-term data on 3 site-specific batches.	First 3 production batches on long-term and accelerated stability studies.
Any dosage form where sufficient primary stability data are not available	6 months of accelerated and 12 months of long-term data on 3 site-specific batches.	First 3 production batches on long-term and accelerated stability studies.

^a The phrase *sufficient primary stability data* means that, at the time of submission, there are 6 months of accelerated data and at least 12 months of long-term data on three primary stability batches made at a different pilot or production site from the intended site.

^b Additional long-term stability data and, if applicable, accelerated data should be submitted for review as soon as they become available prior to the approval.

^c A commitment should be provided in the application to place the first 3 production batches at each site on long-term and accelerated stability studies and annual batches thereafter on long-term studies using the approved protocol and to report the resulting data in annual reports.

Other factors, such as lack of experience at the new site in a particular dosage form, or difference in the environmental conditions between the sites, can potentially affect the quality and/or stability of a drug product. Therefore, one site-specific batch may not be sufficient in these cases. More than one site-specific batch may be needed for a drug substance/product that is intrinsically unstable.

Although one site-specific batch may be sufficient under certain situations, the data so generated, particularly if limited to accelerated studies, may not be amenable to statistical analysis for the establishment of a retest period or expiration dating period. Instead, the single site-specific batch may only serve to verify the stability profile of a drug substance/product that has been established based on primary stability batches at a pilot plant.

In general, site-specific drug product batches should be made with identifiable site-specific drug substance batches both for original applications, wherever possible, and for postapproval stability commitment.

Although pilot and commercial facilities may or may not be located on the same campus or

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1913 within the same geographical area, they will generally employ similar processes and
1914 equipment of the same design and operating principles. If different processes and/or
1915 equipment are used, more site-specific batches and/or longer duration of data are
1916 recommended. If the pilot plant where the primary stability batches are made is located at
1917 the intended commercial site (i.e., on the same campus as the intended manufacturing-scale
1918 production facility) the site-specific stability recommendations are met (provided the
1919 processes and equipment are the same) and no additional data will be needed. A
1920 commitment should be made to place the first three production batches on accelerated and
1921 long-term stability studies. If more than one manufacturing-scale production site is
1922 proposed for an original NDA, BLA or PLA, the recommendations above would be
1923 applicable to each site.

1924 3. Site-Specific Data Package Recommendations for ANDAs

1925 For ANDAs, the primary batch(es) to support the application are usually manufactured in
1926 the production facility. If the primary stability batch(es) are not made at the intended
1927 commercial site, stability data should be generated, as outlined in Table 13, on the drug
1928 product manufactured at that site, i.e. site-specific batches, and the data should be included
1929 in the original submission to demonstrate that the product made at each site is equivalent.

1930 If the pilot plant where the primary stability batches are made is located at the intended
1931 commercial site (i.e., on the same campus as the intended commercial facility), the
1932 site-specific stability recommendations are met and no additional data will be needed. A
1933 commitment should be made to place the first three production batches and annual batches
1934 thereafter on long-term stability studies.

1935 For complex dosage forms as described in the previous section, a reduced number of
1936 site-specific batches may be justified if accelerated and long-term data are available at the
1937 time of application submission on batches made at a different pilot or commercial site from
1938 the intended commercial facility.
1939

1940 **Table 13: Site-Specific Stability Data for a Drug Product in an Original ANDA**

Scenario	Site-Specific Stability Data Recommended at Time of Submission ^a	Stability Commitment ^b
Simple Dosage Form	3 months of accelerated and available long-term data on 1 site-specific batch.	First 3 production batches on long-term stability studies.
Complex Dosage Form	3 months of accelerated and available long-term data on 3 site-specific batches.	First 3 production batches on long-term stability studies.

1946 ^a Drug substance batches used to produce site-specific drug product batches should be clearly identified. Additional
 1947 long-term stability data should be submitted for review as soon as they become available prior to approval.

1948 ^b A commitment should be provided in the application to place the first three production batches at each site on long-
 1949 term stability studies and annual batches thereafter on long-term studies using the approved protocol and to report
 1950 the resulting data in annual reports.

1951 **J. Photostability**

1952 1. General

1953 *The ICH Harmonized Tripartite Guideline on Stability Testing of New Drug Substances and*
 1954 *Products* (hereafter referred to as the *parent guidance*) notes that light testing should be an
 1955 integral part of stress testing.

1956 The ICH Q1B guidance *Photostability Testing of New Drug Substances and Products* primarily
 1957 addresses the generation of photostability information for new molecular entities and associated
 1958 drug products and the use of the data in determining whether precautionary measures in
 1959 manufacturing, labeling, or packaging are needed to mitigate exposure to light. Q1B does not
 1960 specifically address other photostability studies that may be needed to support, for example, the
 1961 photostability of a product under in-use conditions or the photostability of analytical samples.
 1962 Because data are generated on a directly exposed drug substance alone and/or in simple solutions
 1963 and drug products when studies are conducted as described in the Q1B guidance, knowledge of
 1964 photostability characteristics may be useful in determining when additional studies may be needed
 1965 or in providing justification for not performing additional studies. For example, if a product has
 1966 been determined to photodegrade upon direct exposure but is adequately protected by packaging,
 1967 an in-use study may be needed to support the use of the product (e.g., a parenteral drug that is
 1968 infused over a period of time). The test conditions for in-use studies will vary depending on the
 1969 product and use but should depend on and relate to the directions for use of the particular product.

1970 Photostability studies are usually conducted only in conjunction with the first approval of a new
 1971 molecular entity. Under some circumstances, photostability studies should be repeated if certain
 1972 postapproval or supplemental changes, such as changes in formulation or packaging, are made to

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1973 the product, or if a new dosage form is proposed. Whether these studies should be repeated
1974 depends on the photostability characteristics determined at the time of initial filing and the type of
1975 changes made. For example, if initial studies demonstrate that an active moiety in a simple solution
1976 degrades upon exposure to light and the tablet drug product is stable, a subsequent filing
1977 requesting approval of a liquid dosage form may warrant additional studies to characterize the
1978 photostability characteristics of the new dosage form.

1979 Photostability studies need not be conducted for products that duplicate a commercially available
1980 listed drug product provided that the packaging (immediate container/closure and market pack)
1981 and labeling storage statements regarding light duplicate those of the reference listed drug. If
1982 deviations in packaging or labeling statements are made, additional studies may be recommended.
1983 The decision as to whether additional studies should be conducted will be made on a case-by-case
1984 basis by the chemistry review team.

1985 The intrinsic photostability characteristics of new drug substances and products should be
1986 evaluated to demonstrate that, as appropriate, light exposure does not result in unacceptable
1987 change. Normally, photostability testing is carried out on a single batch of material selected as
1988 described in the section Selection of Batches, in the parent guidance. Under some circumstances,
1989 these studies should be repeated if certain variations and changes are made to the product (e.g.,
1990 formulation, packaging). Whether these studies should be repeated depends on the photostability
1991 characteristics determined at the time of initial filing and the type of variation and/or change made.
1992 [ICH Q1B]

1993 A systematic approach to photostability testing is recommended covering, as appropriate, studies
1994 such as:

- 1995 • Tests on the drug substance;
- 1996 • Tests on the exposed drug product outside of the immediate pack; and if necessary,
- 1997 • Tests on the drug product in the immediate pack; and if necessary,
- 1998 • Tests on the drug product in the marketing pack.[ICH Q1B]

1999 The extent of drug product testing should be established by assessing whether or not acceptable
2000 change has occurred at the end of the light exposure testing as described in Figure 2, the Decision
2001 Flow Chart for Photostability Testing of Drug Products. Acceptable change is change within limits
2002 justified by the applicant. [ICH Q1B]

2003 The formal labeling requirements for photolabile drug substances and drug products are established
2004 by national/regional requirements. [ICH Q1B]

2005 2. Light Sources

2006 The light sources described below may be used for photostability testing. The applicant should
2007 either maintain an appropriate control of temperature to minimize the effect of localized
2008 temperature changes or include a dark control in the same environment unless otherwise justified.
2009 For both options 1 and 2, a pharmaceutical manufacturer/applicant can rely on the spectral
2010 distribution specification of the light source manufacturer. [ICH Q1B]
2011

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2012 **Option 1**

2013 Any light source that is designed to produce an output similar to the D65/ID65 emission standard
2014 such as an artificial daylight fluorescent lamp combining visible and ultraviolet (UV) outputs,
2015 xenon, or metal halide lamp. D65 is the internationally recognized standard for outdoor daylight as
2016 defined in ISO 10977 (1993). ID65 is the equivalent indoor indirect daylight standard. For a light
2017 source emitting significant radiation below 320 nanometers (nm), an appropriate filter(s) may be
2018 fitted to eliminate such radiation. [ICHQ1B]

2019 **Option 2**

2020 For option 2 the same sample should be exposed to both the cool white fluorescent and near
2021 ultraviolet lamp.

- 2022 • A cool white fluorescent lamp designed to produce an output similar to that specified in ISO
2023 10977 (1993); and
- 2024 • A near UV fluorescent lamp having a spectral distribution from 320 nm to 400 nm with a
2025 maximum energy emission between 350 nm and 370 nm; a significant proportion of UV should
2026 be in both bands of 320 to 360 nm and 360 to 400 nm. [ICH Q1B]

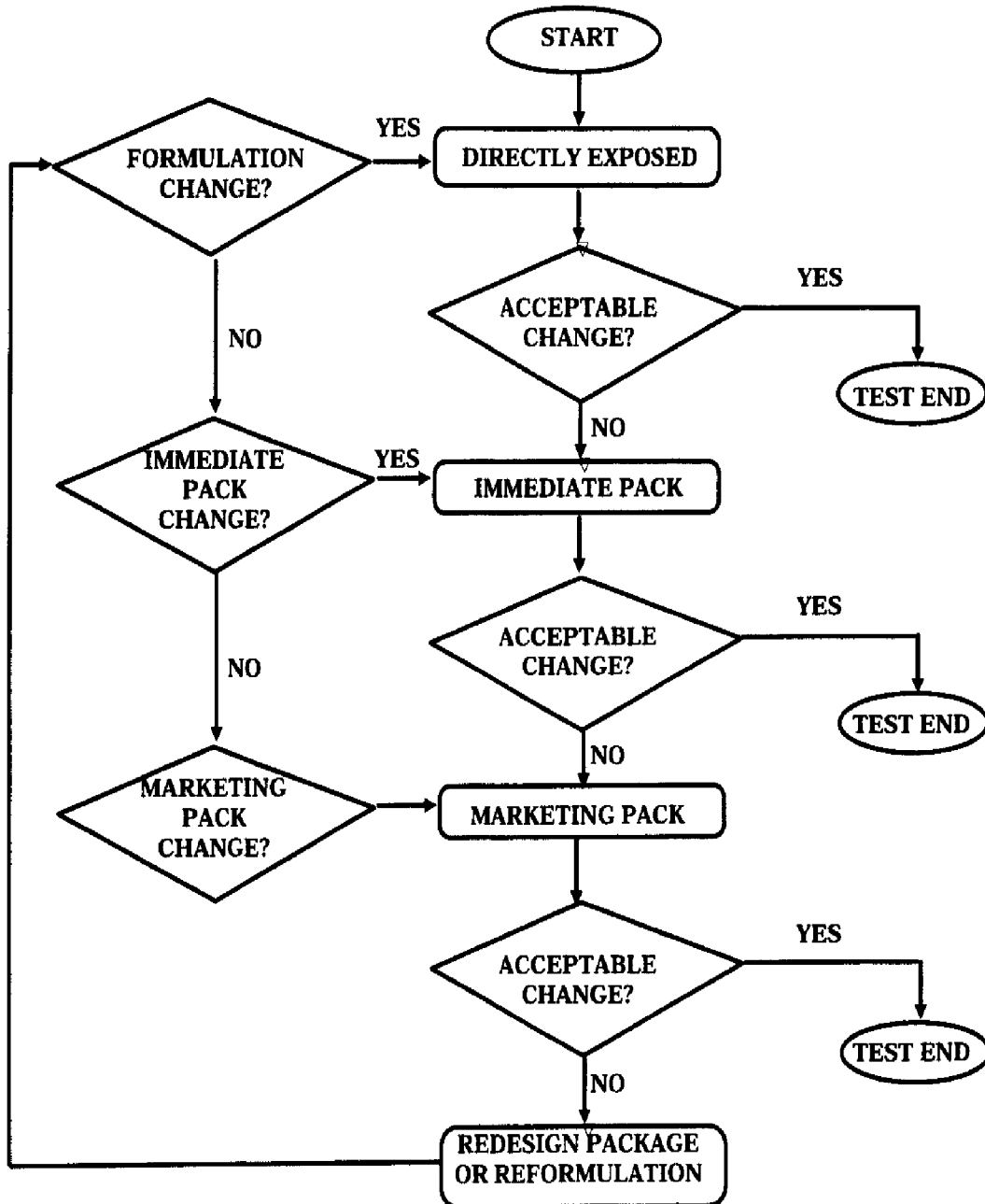
2027
2028 3. Procedure [ICH Q1B]

2029 For confirmatory studies, samples should be exposed to light providing an overall illumination of
2030 not less than 1.2 million lux hours and an integrated near ultraviolet energy of not less than 200
2031 watt hours/square meter to allow direct comparisons to be made between the drug substance and
2032 drug product.

2033 Samples may be exposed side-by-side with a validated chemical actinometric system to ensure the
2034 specified light exposure is obtained, or for the appropriate duration of time when conditions have
2035 been monitored using calibrated radiometers/lux meters. An example of an actinometric procedure
2036 is provided in the Annex.

2037 If protected samples (e.g., wrapped in aluminum foil) are used as dark controls to evaluate the
2038 contribution of thermally induced change to the total observed change, these should be placed
2039 alongside the authentic sample. [ICH Q1B]

DECISION FLOW CHART FOR
PHOTOSTABILITY TESTING
OF DRUG PRODUCTS



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2040 4. Drug Substance [ICH Q1B]

2041 For drug substances, photostability testing should consist of two parts: Forced degradation testing
2042 and confirmatory testing.

2043 The purpose of forced degradation testing studies is to evaluate the overall photosensitivity of the
2044 material for method development purposes and/or degradation pathway elucidation. This testing
2045 may involve the drug substance alone and/or in simple solutions/suspensions to validate the
2046 analytical procedures. In these studies, the samples should be in chemically inert and transparent
2047 containers. In these forced degradation studies, a variety of exposure conditions may be used,
2048 depending on the photosensitivity of the drug substance involved and the intensity of the light
2049 sources used. For development and validation purposes, it is appropriate to limit exposure and end
2050 the studies if extensive decomposition occurs. For photostable materials, studies may be
2051 terminated after an appropriate exposure level has been used. The design of these experiments is
2052 left to the applicant's discretion although the exposure levels used should be justified.

2053 Under forcing conditions, decomposition products may be observed that are unlikely to be formed
2054 under the conditions used for confirmatory studies. This information may be useful in developing
2055 and validating suitable analytical methods. If in practice it has been demonstrated they are not
2056 formed in the confirmatory studies, these degradation products need not be examined further.

2057 Confirmatory studies should then be undertaken to provide the information necessary for handling,
2058 packaging, and labeling (see Section VIII.J.3., Procedure, and 4.a., Presentation of Samples, for
2059 information on the design of these studies).

2060 Normally, only one batch of drug substance is tested during the development phase, and then the
2061 photostability characteristics should be confirmed on a single batch selected as described in the
2062 parent guidance if the drug is clearly photostable or photolabile. If the results of the confirmatory
2063 study are equivocal, testing of up to two additional batches should be conducted. Samples should
2064 be selected as described in the parent guidance.

2065 a. Presentation of Samples [ICH Q1B]

2066 Care should be taken to ensure that the physical characteristics of the samples under test are taken
2067 into account, and efforts should be made, such as cooling and/or placing the samples in sealed
2068 containers, to ensure that the effects of the changes in physical states such as sublimation,
2069 evaporation, or melting are minimized. All such precautions should be chosen to provide minimal
2070 interference with the exposure of samples under test. Possible interactions between the samples
2071 and any material used for containers or for general protection of the sample should also be
2072 considered and eliminated wherever not relevant to the test being carried out.

2073 As a direct challenge for samples of solid drug substances, an appropriate amount of sample should
2074 be taken and placed in a suitable glass or plastic dish and protected with a suitable transparent
2075 cover if considered necessary. Solid drug substances should be spread across the container to give

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2076 a thickness of typically not more than 3 millimeters. Drug substances that are liquids should be
2077 exposed in chemically inert and transparent containers.

2078 b. Analysis of Samples

2079 At the end of the exposure period, the samples should be examined for any changes in physical
2080 properties (e.g., appearance, clarity or color of solution) and for assay and degradants by a method
2081 suitably validated for products likely to arise from photochemical degradation processes.

2082 Where solid drug substance samples are involved, sampling should ensure that a representative
2083 portion is used in individual tests. Similar sampling considerations, such as homogenization of the
2084 entire sample, apply to other materials that may not be homogeneous after exposure. The analysis
2085 of the exposed sample should be performed concomitantly with that of any protected samples used
2086 as dark control if these are used in the test.

2087 c. Judgment of Results

2088 The forced degradation studies should be designed to provide suitable information to develop and
2089 validate test methods for the confirmatory studies. These test methods should be capable of
2090 resolving and detecting photolytic degradants that appear during the confirmatory studies. When
2091 evaluating the results of these studies, it is important to recognize that they form part of the stress
2092 testing and are not therefore designed to establish qualitative or quantitative limits for change.

2093 The confirmatory studies should identify precautionary measures needed in manufacturing or in
2094 formulation of the drug product and if light resistant packaging is needed. When evaluating the
2095 results of confirmatory studies to determine whether change due to exposure to light is acceptable,
2096 it is important to consider the results from other formal stability studies to ensure that the drug will
2097 be within justified limits at time of use (see the relevant ICH stability and impurity guidance).

2098 5. Drug Product [ICH Q1B]

2099 Normally, the studies on drug products should be carried out in a sequential manner starting with
2100 testing the fully exposed product then progressing as necessary to the product in the immediate
2101 pack and then in the marketing pack. Testing should progress until the results demonstrate that
2102 the drug product is adequately protected from exposure to light. The drug product should be
2103 exposed to the light conditions described under the procedure in Section VII.J.3.
2104

2105 Normally, only one batch of drug product is tested during the development phase, and then the
2106 photostability characteristics should be confirmed on a single batch selected as described in the
2107 parent guidance if the product is clearly photostable or photolabile. If the results of the
2108 confirmatory study are equivocal, testing of up to two additional batches should be conducted.

2109 For some products where it has been demonstrated that the immediate pack is completely
2110 impenetrable to light, such as aluminum tubes or cans, testing should normally only be conducted
2111 on directly exposed drug product.

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2112 It may be appropriate to test certain products, such as infusion liquids or dermal creams, to
2113 support their photostability in-use. The extent of this testing should depend on and relate to the
2114 directions for use, and is left to the applicant's discretion.

2115 The analytical procedures used should be suitably validated.

2116 a. Presentation of Samples

2117 Care should be taken to ensure that the physical characteristics of the samples under test are taken
2118 into account, and efforts, such as cooling and/or placing the samples in sealed containers, should
2119 be made to ensure that the effects of the changes in physical states are minimized, such as
2120 sublimation, evaporation, or melting. All such precautions should be chosen to provide minimal
2121 interference with the irradiation of samples under test. Possible interactions between the samples
2122 and any material used for containers or for general protection of the sample should also be
2123 considered and eliminated wherever not relevant to the test being carried out.

2124 Where practicable when testing samples of the drug product outside of the primary pack, these
2125 should be presented in a way similar to the conditions mentioned for the drug substance. The
2126 samples should be positioned to provide maximum area of exposure to the light source. For
2127 example, tablets and capsules should be spread in a single layer.

2128 If direct exposure is not practical (e.g., due to oxidation of a product), the sample should be placed
2129 in a suitable protective inert transparent container (e.g., quartz).

2130 If testing of the drug product in the immediate container or as marketed is needed, the samples
2131 should be placed horizontally or transversely with respect to the light source, whichever provides
2132 for the most uniform exposure of the samples. Some adjustment of testing conditions may have to
2133 be made when testing large volume containers (e.g., dispensing packs).

2134 b. Analysis of Samples

2135 At the end of the exposure period, the samples should be examined for any changes in physical
2136 properties (e.g., appearance, clarity, or color of solution, dissolution/disintegration for dosage
2137 forms such as capsules) and for assay and degradants by a method suitably validated for products
2138 likely to arise from photochemical degradation processes.

2139 When powder samples are involved, sampling should ensure that a representative portion is used in
2140 individual tests. For solid oral dosage form products, testing should be conducted on an
2141 appropriately sized composite of, for example, 20 tablets or capsules. Similar sampling
2142 considerations, such as homogenization or solubilization of the entire sample, apply to other
2143 materials that may not be homogeneous after exposure (e.g., creams, ointments, suspensions). The
2144 analysis of the exposed sample should be performed concomitantly with that of any protected
2145 samples used as dark controls if these are used in the test.

2146 c. Judgment of Results

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2147 Depending on the extent of change, special labeling or packaging may be needed to mitigate
2148 exposure to light. When evaluating the results of photostability studies to determine whether
2149 change due to exposure to light is acceptable, it is important to consider the results obtained from
2150 other formal stability studies to ensure that the product will be within proposed specifications
2151 during the shelf life (see the relevant ICH stability and impurity guidance).

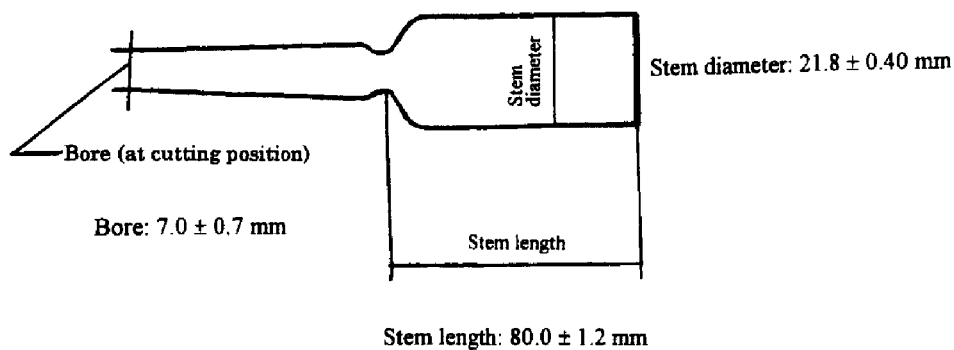
2152 **6. Quinine Chemical Actinometry [ICH Q1B]**

2153 The following provides details of an actinometric procedure for monitoring exposure to a near UV
2154 fluorescent lamp (based on work done by FDA/National Institute of Standards and Technology
2155 study). For other light sources/actinometric systems, the same approach may be used, but each
2156 actinometric system should be calibrated for the light source used.

2157 Prepare a sufficient quantity of a 2 percent weight/volume aqueous solution of quinine
2158 monohydrochloride dihydrate (if necessary, dissolve by heating).

2159 **Option 1**
2160

2161 Put 10 milliliters (mL) of the solution into a 20 mL colorless ampoule (see drawing, below), seal it
2162 hermetically, and use this as the sample. Separately, put 10 mL of the solution into a 20 mL
2163 colorless ampoule (see note 1), seal it hermetically, wrap in aluminum foil to protect completely
2164 from light, and use this as the control. Expose the sample and control to the light source for an
2165 appropriate number of hours. After exposure, determine the absorbances of the sample (AT) and
2166 the control (AO) at 400 nm using a 1 centimeter (cm) path length. Calculate the change in
2167 absorbance units (AU): $A = AT - AO$. The length of exposure should be sufficient to ensure a
2168 change in absorbance of at least 0.9 AU. *Note: Shape and Dimensions (See Japanese Industry*
2169 *Standard (JIS) R3512 (1974) for ampoule specifications).*¹⁰



¹⁰ Yoshioka, S., "Quinine Actinometry as a Method for Calibrating Ultraviolet Radiation Intensity in Light-stability Testing of Pharmaceuticals," *Drug Development and Industrial Pharmacy*, 20(13):2049-2062, 1994

2170 **Option 2**

2171 Fill a 1 cm quartz cell and use this as the sample. Separately fill a 1 cm quartz cell, wrap in
2172 aluminum foil to protect completely from light, and use this as the control. Expose the sample and
2173 control to the light source for an appropriate number of hours. After exposure, determine the
2174 absorbances of the sample (AT) and the control (AO) at 400 nm. Calculate the change in
2175 absorbance, $\Delta A = AT - AO$. The length of exposure should be sufficient to ensure a change in
2176 absorbance of at least 0.5.

2177 Alternative packaging configurations may be used if appropriately validated. Alternative validated
2178 chemical actinometers may be used.

2179 7. Acceptable/Unacceptable Photostability Change

2180 The extent of the drug product photostability testing depends on the change that has occurred at
2181 the end of each test tier described in Figure 2, above, the Decision Flow Chart for Photostability
2182 Testing of Drug Products. Test results that are outside the proposed acceptance criteria for the
2183 product would not be considered acceptable change. This is a stress test designed to determine the
2184 intrinsic photostability characteristics of new drug substances and products, and no correlation has
2185 been developed to equate a within specification result to an expiration dating period. The
2186 acceptability of any observed changes should be justified in the application. It may be important to
2187 consider other degradative processes (e.g., thermal) when justifying a photostability change as
2188 acceptable because the processes may be independent and additive. For example, a 5 percent loss
2189 in potency due to photodegradation may be considered acceptable if that is the only type of
2190 degradation observed. If the product is also expected to degrade 5 percent over the shelf-life due
2191 to thermal degradation, the photodegradation may then be considered unacceptable based on the
2192 potential additive effect of the changes. In this case, precautions should be taken to mitigate the
2193 product's exposure to light.

2194 Under the intense light exposure conditions included in the Q1B guidance, certain colors in solid
2195 dosage forms may fade. Quantitative analysis of the color change is not recommended as these
2196 changes are not likely to occur under actual storage conditions. In the absence of change in other
2197 parameters such as assay, these color changes may be acceptable.

2198
2199 8. Photostability Labeling Considerations
2200

2201 The data generated using the procedure described in the ICH Q1A guidance is useful in
2202 determining when special handling or storage statements regarding exposure to light should be
2203 included in the product labeling (21 CFR 201.57(k)(4)). The labeling guidance provided below
2204 pertains only to products as packaged for distribution. Instructions and stability statements that
2205 may be needed to address in-use conditions pursuant to 21 CFR 201.57(j) are not covered.

2206 **Change after direct exposure:** If changes that are observed when the product is directly exposed

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2207 under the light conditions described in the Q1B guidance are acceptable, no labeling storage
2208 statement regarding light is needed.

2209 **Change after exposure in the immediate container/closure:** If changes observed when the
2210 product is directly exposed are unacceptable, but are acceptable when the product is tested in the
2211 immediate container/closure under the conditions described in the Q1B guidance, the inclusion of a
2212 labeling storage statement regarding light would depend on the likelihood of the product being
2213 removed from the immediate package during the distribution process.

2214 • For those products that are unlikely to be removed from the immediate container, such as
2215 creams or ointments in tubes dispensed directly to the patient, and ophthalmic products, the
2216 use of a labeling storage statement regarding light is optional.

2217 • For products that may be removed from the immediate pack, such as pharmacy bulk packs, a
2218 light storage statement should be included such as “PROTECT FROM LIGHT. Dispense in a
2219 light-resistant container.”

2220 **Change after exposure in the market pack:** If changes that are observed are acceptable only
2221 when the product in the market pack is exposed under the conditions described in the Q1B
2222 guidance, labeling storage statements regarding light should be included.
2223

2224 Examples of typical storage statements are, for single-dose and multiple-dose products
2225 respectively, “PROTECT FROM LIGHT. Retain in carton until time of use.” and “PROTECT
2226 FROM LIGHT. Retain in carton until contents are used.”

2227 **K. Degradation Products**

2228 When degradation products are detected upon storage, the following information about them
2229 should be submitted:

- 2230 • Procedure for isolation and purification
- 2231 • Identity and chemical structures
- 2232 • Degradation pathways
- 2233 • Physical and chemical properties
- 2234 • Detection and quantitation levels
- 2235 • Acceptance Criteria (individual and total)
- 2236 • Test methods
- 2237 • Validation data
- 2238 • Biological effect and pharmacological actions, including toxicity studies, at the concentrations
2239 likely to be encountered (cross-reference to any available information is acceptable)

2240 If racemization of the drug substance in the dosage form is possible, the information described
2241 above also should be provided.

2242 **L. Thermal Cycling**

2243 A study of the effects of temperature variation, particularly if appropriate for the shipping and

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2244 storage conditions of certain drug products, should be considered. Drug products susceptible to
2245 phase separation, loss of viscosity, precipitation, and aggregation should be evaluated under such
2246 thermal conditions. As part of the stress testing, the packaged drug product should be cycled
2247 through temperature conditions that simulate the changes likely to be encountered once the drug
2248 product is in distribution.

2249 • A temperature cycling study for drug products that may be exposed to temperature variations
2250 above freezing may consist of three cycles of two days at refrigerated temperature (2-8°C)
2251 followed by two days under accelerated storage conditions (40°C).

2252 • A temperature cycling study for drug products that may be exposed to sub-freezing
2253 temperatures may consist of three cycles of two days at freezer temperature (-10° to -20°C)
2254 followed by two days under accelerated storage conditions (40°C).

2255 • For inhalation aerosols, the recommended cycle study consists of three or four six-hour cycles
2256 per day, between subfreezing temperature and 40°C (75-85 percent RH) for a period of up to
2257 six weeks.

2258 • For frozen drug products, the recommended cycle study should include an evaluation of effects
2259 due to accelerated thawing in a microwave or a hot water bath unless contraindicated in the
2260 labeling.

2261 • Alternatives to these conditions may be acceptable with appropriate justification.

2262 **M. Stability Testing in Foreign Laboratory Facilities**

2263 Stability testing (as well as finished product release testing) performed in any foreign or domestic
2264 facility may be used as the basis for approval of an application. This includes all NDAs, ANDAs,
2265 and related CMC supplements. A satisfactory inspection of the laboratory(ies) that will perform
2266 the testing will be necessary.¹¹

2267 Applicants should consider the effects of bulk packaging, shipping, and holding of dosage forms
2268 and subsequent market packaging, and distribution of the finished drug product, and be aware of
2269 the effect of such operations on product quality. Time frames should be established to encompass
2270 the date of production, date of quality control release of the dosage form, bulk packaging,
2271 shipping, and market packaging, and initiation and performance of the stability studies on the drug
2272 product should be established, controlled, and strictly followed. Maximum time frames for each
2273 operation should be established and substantiated by the applicant.

¹¹ This statement replaces a previous position, established via a CDER Office of Generic Drugs guidance, which recommended that finished product and stability testing be conducted at a United States laboratory for drug products manufactured in foreign facilities and shipped in bulk containers to the United States for packaging into immediate containers for marketing.

2274 **N. Stability Testing of Biotechnology Drug Products**

2275 1. General [ICH Q5C]

2276 The ICH harmonized tripartite guidance entitled *Q1A Stability Testing of New Drug Substances*
2277 *and Products* issued by ICH on October 27, 1993, applies in general to biotechnological/biological
2278 products. However, biotechnological/biological products have distinguishing characteristics to
2279 which consideration should be given in any well-defined testing program designed to confirm their
2280 stability during the intended storage period. For such products in which the active components are
2281 typically proteins and/or polypeptides, maintenance of molecular conformation and, hence, of
2282 biological activity, is dependent on noncovalent as well as covalent forces. The products are
2283 particularly sensitive to environmental factors such as temperature changes, oxidation, light, ionic
2284 content, and shear. To ensure maintenance of biological activity and to avoid degradation,
2285 stringent conditions for their storage are usually necessary.

2286 The evaluation of stability may necessitate complex analytical methodologies. Assays for
2287 biological activity, where applicable, should be part of the pivotal stability studies. Appropriate
2288 physicochemical, biochemical, and immunochemical methods for the analysis of the molecular
2289 entity and the quantitative detection of degradation products should also be part of the stability
2290 program whenever purity and molecular characteristics of the product permit use of these
2291 methodologies.

2292 With these concerns in mind, the applicant should develop the proper supporting stability data for a
2293 biotechnological/biological product and consider many external conditions that can affect the
2294 product's potency, purity, and quality. Primary data to support a requested storage period for
2295 either drug substance or drug product should be based on long-term, real-time, real-condition
2296 stability studies. Thus, the development of a proper long-term stability program becomes critical to
2297 the successful development of a commercial product. The purpose of this document is to give
2298 guidance to applicants regarding the type of stability studies that should be provided in support of
2299 marketing applications. It is understood that during the review and evaluation process, continuing
2300 updates of initial stability data may occur.

2301 2. Scope [ICH Q5C]

2302 The guidance in this section applies to well-characterized proteins and polypeptides, their
2303 derivatives and products of which they are components and which are isolated from tissues, body
2304 fluids, cell cultures, or produced using recombinant deoxyribonucleic acid (r-DNA) technology.
2305 Thus, the section covers the generation and submission of stability data for products such as
2306 cytokines (interferons, interleukins, colony-stimulating factors, tumor necrosis factors),
2307 erythropoietins, plasminogen activators, blood plasma factors, growth hormones and growth
2308 factors, insulins, monoclonal antibodies, and vaccines consisting of well-characterized proteins or
2309 polypeptides. In addition, the guidance outlined in the following sections may apply to other types
2310 of products, such as conventional vaccines, after consultation with the product review office. The
2311 section does not cover antibiotics, allergenic extracts, heparins, vitamins, whole blood, or cellular
2312 blood components.

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2313 3. Terminology [ICH Q5C]

2314 For the basic terms used in this section, the reader is referred to the Glossary. However, because
2315 manufacturers of biotechnological/biological products sometimes use traditional terminology,
2316 traditional terms are specified in parentheses to assist the reader.

2317 4. Selection of Batches [ICH Q5C]

2318 a. Drug Substance (Bulk Material)

2319 Where bulk material is to be stored after manufacture, but before formulation and final
2320 manufacturing, stability data should be provided on at least three batches for which manufacture
2321 and storage are representative of the manufacturing scale of production. A minimum of six
2322 months' stability data at the time of submission should be submitted in cases where storage periods
2323 greater than six months are requested. For drug substances with storage periods of less than six
2324 months, the minimum amount of stability data in the initial submission should be determined on a
2325 case-by-case basis. Data from pilot-scale batches of drug substance produced at a reduced scale of
2326 fermentation and purification may be provided at the time the application is submitted to the
2327 Agency with a commitment to place the first three manufacturing scale batches into the long-term
2328 stability program after approval.

2329 The quality of the batches of drug substance placed into the stability program should be
2330 representative of the quality of the material used in preclinical and clinical studies and of the quality
2331 of the material to be made at manufacturing scale. In addition, the drug substance (bulk material)
2332 made at pilot-scale should be produced by a process and stored under conditions representative of
2333 that used for the manufacturing scale. The drug substance entered into the stability program should
2334 be stored in containers that properly represent the actual holding containers used during
2335 manufacture. Containers of reduced size may be acceptable for drug substance stability testing
2336 provided that they are constructed of the same material and use the same type of container/closure
2337 system that is intended to be used during manufacture.

2338 b. Intermediates

2339 During manufacture of biotechnological/biological products, the quality and control of certain
2340 intermediates may be critical to the production of the final product. In general, the manufacturer
2341 should identify intermediates and generate in-house data and process limits that ensure their
2342 stability within the bounds of the developed process. Although the use of pilot-scale data is
2343 permissible, the manufacturer should establish the suitability of such data using the manufacturing-
2344 scale process.

2345 c. Drug Product (Final Container Product)

2346 Stability information should be provided on at least three batches of final container product
2347 representative of that which will be used at manufacturing scale. Where possible, batches of final
2348 container product included in stability testing should be derived from different batches of bulk
2349 material. A minimum of six months' data at the time of submission should be submitted in cases

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2350 where storage periods greater than six months are requested. For drug products with storage
2351 periods of less than six months, the minimum amount of stability data in the initial submission
2352 should be determined on a case-by-case basis. Product expiration dating should be based upon the
2353 actual data submitted in support of the application. Because dating is based upon the
2354 real-time/real-temperature data submitted for review, continuing updates of initial stability data
2355 should occur during the review and evaluation process. The quality of the final container product
2356 placed on stability studies should be representative of the quality of the material used in the
2357 preclinical and clinical studies. Data from pilot-scale batches of drug product may be provided at
2358 the time the application is submitted to the Agency with a commitment to place the first three
2359 manufacturing scale batches into the long-term stability program after approval. Where pilot-plant
2360 scale batches were submitted to establish the dating for a product and, in the event that the product
2361 produced at manufacturing scale does not meet those long-term stability specifications throughout
2362 the dating period or is not representative of the material used in preclinical and clinical studies, the
2363 applicant should notify the appropriate FDA reviewing office to determine a suitable course of
2364 action.

2365 d. Sample Selection

2366 Where one product is distributed in batches differing in fill volume (e.g., 1 milliliter (mL), 2 mL, or
2367 10 mL), unitage (e.g., 10 units, 20 units, or 50 units), or mass (e.g., 1 milligram (mg), 2 mg, or 5
2368 mg), samples to be entered into the stability program may be selected on the basis of a matrix
2369 system and/or by bracketing.

2370 Matrixing — the statistical design of a stability study in which different fractions of samples are
2371 tested at different sampling points — should only be applied when appropriate documentation is
2372 provided that confirms that the stability of the samples tested represents the stability of all samples.
2373 The differences in the samples for the same drug product should be identified as, for example,
2374 covering different batches, different strengths, different sizes of the same closure, and, possibly, in
2375 some cases, different container/closure systems. Matrixing should not be applied to samples with
2376 differences that may affect stability, such as different strengths and different containers/closures,
2377 where it cannot be confirmed that the products respond similarly under storage conditions,

2378 Where the same strength and exact container/closure system is used for three or more fill contents,
2379 the manufacturer may elect to place only the smallest and largest container size into the stability
2380 program (i.e., bracketing). The design of a protocol that incorporates bracketing assumes that the
2381 stability of the intermediate condition samples are represented by those at the extremes. In certain
2382 cases, data may be needed to demonstrate that all samples are properly represented by data
2383 collected for the extremes.

2384 5. Stability-Indicating Profile [ICH Q5C]

2385 On the whole, there is no single stability-indicating assay or parameter that profiles the stability
2386 characteristics of a biotechnological/biological product. Consequently, the manufacturer should
2387 propose a stability-indicating profile that provides assurance that changes in the identity, purity,
2388 and potency of the product will be detected.

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2389 At the time of submission, applicants should have validated the methods that comprise the
2390 stability-indicating profile, and the data should be available for review. The determination of which
2391 tests should be included will be product-specific. The items emphasized in the following
2392 subsections are not intended to be all-inclusive, but represent product characteristics that should
2393 typically be documented to demonstrate product stability adequately.

2394 a. Protocol

2395 The marketing application should include a detailed protocol for the assessment of the stability of
2396 both drug substance and drug product in support of the proposed storage conditions and
2397 expiration dating periods. The protocol should include all necessary information that demonstrates
2398 the stability of the biotechnological/biological product throughout the proposed expiration dating
2399 period including, for example, well-defined specifications and test intervals. The statistical methods
2400 that should be used are described in the ICH Q1A guidance on stability.

2401 b. Potency

2402 When the intended use of a product is linked to a definable and measurable biological activity,
2403 testing for potency should be part of the stability studies. For the purpose of stability testing of the
2404 products described in this guidance, potency is the specific ability or capacity of a product to
2405 achieve its intended effect. It is based on the measurement of some attribute of the product and is
2406 determined by a suitable in vivo or in vitro quantitative method. In general, potencies of
2407 biotechnological/biological products tested by different laboratories can be compared in a
2408 meaningful way only if expressed in relation to that of an appropriate reference material. For that
2409 purpose, a reference material calibrated directly or indirectly against the corresponding national or
2410 international reference material should be included in the assay.

2411 Potency studies should be performed at appropriate intervals as defined in the stability protocol
2412 and the results should be reported in units of biological activity calibrated, whenever possible,
2413 against nationally or internationally recognized standards. Where no national or international
2414 reference standards exist, the assay results may be reported in in-house derived units using a
2415 characterized reference material.

2416 In some biotechnological/biological products, potency is dependent upon the conjugation of the
2417 active ingredient(s) to a second moiety or binding to an adjuvant. Dissociation of the active
2418 ingredient(s) from the carrier used in conjugates or adjuvants should be examined in
2419 real-time/real-temperature studies (including conditions encountered during shipment). The
2420 assessment of the stability of such products may be difficult because, in some cases, in vitro tests
2421 for biological activity and physicochemical characterization are impractical or provide inaccurate
2422 results. Appropriate strategies (e.g., testing the product before conjugation/binding, assessing the
2423 release of the active compound from the second moiety, in vivo assays) or the use of an
2424 appropriate surrogate test should be considered to overcome the inadequacies of in vitro testing.

2425 c. Purity and Molecular Characterization

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2426 For the purpose of stability testing of the products described in this guidance, purity is a relative
2427 term. Because of the effect of glycosylation, deamidation, or other heterogeneities, the absolute
2428 purity of a biotechnological/biological product is extremely difficult to determine. Thus, the purity
2429 of a biotechnological/biological product should be typically assessed by more than one method and
2430 the purity value derived is method-dependent. For the purpose of stability testing, tests for purity
2431 should focus on methods for determination of degradation products.

2432 The degree of purity, as well as the individual and total amounts of degradation products of the
2433 biotechnological/biological product entered into the stability studies, should be reported and
2434 documented whenever possible. Limits of acceptable degradation should be derived from the
2435 analytical profiles of batches of the drug substance and drug product used in the preclinical and
2436 clinical studies.

2437 The use of relevant physicochemical, biochemical, and immunochemical analytical methodologies
2438 should permit a comprehensive characterization of the drug substance and/or drug product (e.g.,
2439 molecular size, charge, hydrophobicity) and the accurate detection of degradation changes that
2440 may result from deamidation, oxidation, sulfoxidation, aggregation, or fragmentation during
2441 storage. As examples, methods that may contribute to this include electrophoresis (SDS-PAGE,
2442 immunoelectrophoresis, Western blot, isoelectrofocusing), high-resolution chromatography (e.g.,
2443 reversed-phase chromatography, gel filtration, ion exchange, affinity chromatography), and peptide
2444 mapping.

2445 Wherever significant qualitative or quantitative changes indicative of degradation product
2446 formation are detected during long-term, accelerated, and/or stress stability studies, consideration
2447 should be given to potential hazards and to the need for characterization and quantification of
2448 degradation products within the long-term stability program. Acceptable limits should be proposed
2449 and justified, taking into account the levels observed in material used in preclinical and clinical
2450 studies.

2451 For substances that cannot be properly characterized or products for which an exact analysis of the
2452 purity cannot be determined through routine analytical methods, the applicant should propose and
2453 justify alternative testing procedures.

2454 d. Other Product Characteristics

2455 The following product characteristics, though not specifically relating to
2456 biotechnological/biological products should be monitored and reported for the drug product in its
2457 final container:

- 2458 • Visual appearance of the product (color and opacity for solutions/suspensions; color, texture,
2459 and dissolution time for powders), visible particulates in solutions or after the reconstitution of
2460 powders or lyophilized cakes, pH, and moisture level of powders and lyophilized products.
- 2461 • Sterility testing or alternatives (e.g., container/closure integrity testing) should be performed at
2462 a minimum initially and at the end of the proposed shelf life.

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2463 • Additives (e.g., stabilizers, preservatives) or excipients may degrade during the dating period
2464 of the drug product. If there is any indication during preliminary stability studies that reaction
2465 or degradation of such materials adversely affect the quality of the drug product, these items
2466 may need to be monitored during the stability program.

2467 • The container/closure has the potential to affect the product adversely and should be carefully
2468 evaluated (see below).

2469 6. Storage Conditions [ICH Q5C]

2470 a. Temperature

2471 Because most finished biotechnological/biological products need precisely defined storage
2472 temperatures, the storage conditions for the real-time/real-temperature stability studies may be
2473 confined to the proposed storage temperature.

2474 b. Humidity

2475 Biotechnological/biological products are generally distributed in containers protecting them against
2476 humidity. Therefore, where it can be demonstrated that the proposed containers (and conditions of
2477 storage) afford sufficient protection against high and low humidity, stability tests at different
2478 relative humidities can usually be omitted. Where humidity-protecting containers are not used,
2479 appropriate stability data should be provided.

2480 c. Accelerated and Stress Conditions

2481 As previously noted, the expiration dating should be based on real-time/real-temperature data.
2482 However, it is strongly recommended that studies be conducted on the drug substance and drug
2483 product under accelerated and stress conditions. Studies under accelerated conditions may provide
2484 useful support data for establishing the expiration date, provide product stability information or
2485 future product development (e.g., preliminary assessment of proposed manufacturing changes such
2486 as change in formulation, scale-up), assist in validation of analytical methods for the stability
2487 program, or generate information that may help elucidate the degradation profile of the drug
2488 substance or drug product. Studies under stress conditions may be useful in determining whether
2489 accidental exposures to conditions other than those proposed (e.g., during transportation) are
2490 deleterious to the product and also for evaluating which specific test parameters may be the best
2491 indicators of product stability. Studies of the exposure of the drug substance or drug product to
2492 extreme conditions may help to reveal patterns of degradation; if so, such changes should be
2493 monitored under proposed storage conditions. Although the OCH Q1A guidance on stability
2494 describes the conditions of the accelerated and stress study, the applicant should note that those
2495 conditions may not be appropriate for biotechnological/biological products. Conditions should be
2496 carefully selected on a case-by-case basis.

2497 d. Light

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2498 Applicants should consult the FDA on a case-by-case basis to determine guidance for testing.

2499

2500

e. Container/Closure

2501 Changes in the quality of the product may occur due to the interactions between the formulated
2502 biotechnological/biological product and container/closure. Where the lack of interactions cannot be
2503 excluded in liquid products (other than sealed ampules), stability studies should include samples
2504 maintained in the inverted or horizontal position (i.e., in contact with the closure) as well as in the
2505 upright position, to determine the effects of the closure on product quality. Data should be
2506 supplied for all different container/closure combinations that will be marketed.

2507 In addition to the standard data necessary for a conventional single-use vial, the applicant should
2508 demonstrate that the closure used with a multiple-dose vial is capable of withstanding the
2509 conditions of repeated insertions and withdrawals so that the product retains its full potency,
2510 purity, and quality for the maximum period specified in the instructions-for-use on containers,
2511 packages, and/or package inserts. Such labeling should be in accordance with FDA requirements.

2512 f. Stability after Reconstitution of Freeze-Dried Product

2513 The stability of freeze-dried products after their reconstitution should be demonstrated for the
2514 conditions and the maximum storage period specified on containers, packages, and/or package
2515 inserts. Such labeling should be in accordance with FDA requirements.

2516 7. Testing Frequency [ICH Q5C]

2517 The shelf lives of biotechnological/biological products may vary from days to several years. Thus,
2518 it is difficult to draft uniform guidances regarding the stability study duration and testing frequency
2519 that would be applicable to all types of biotechnological/biological products. With only a few
2520 exceptions, however, the shelf lives for existing products and potential future products will be
2521 within the range of 0.5 to 5 years. Therefore, the guidance is based upon expected shelf lives in
2522 that range. This takes into account the fact that degradation of biotechnological/biological
2523 products may not be governed by the same factors during different intervals of a long storage
2524 period.

2525 When shelf lives of one year or less are proposed, the real-time stability studies should be
2526 conducted monthly for the first three months and at three month intervals thereafter. For products
2527 with proposed shelf lives of greater than one year, the studies should be conducted every three
2528 months during the first year of storage, every six months during the second year, and annually
2529 thereafter.

2530 While the testing intervals listed above may be appropriate in the preapproval or prelicense stage,
2531 reduced testing may be appropriate after approval or licensing where data are available that
2532 demonstrate adequate stability. Where data exist that indicate the stability of a product is not
2533 compromised, the applicant is encouraged to submit a protocol that supports elimination of
2534 specific test intervals (e.g., nine-month testing) for postapproval/postlicensing, long-term studies.

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2535 8. Specifications [ICH Q5C]

2536 Although biotechnological/biological products may be subject to significant losses of activity,
2537 physicochemical changes, or degradation during storage, international and national regulations
2538 have provided little guidance with respect to distinct release and end of shelf life specifications.
2539 Recommendations for maximum acceptable losses of activity, limits for physicochemical changes,
2540 or degradation during the proposed shelf life have not been developed for individual types or
2541 groups of biotechnological/biological products but are considered on a case-by-case basis. Each
2542 product should retain its specifications within established limits for safety, purity, and potency
2543 throughout its proposed shelf life. These specifications and limits should be derived from all
2544 available information using the appropriate statistical methods. The use of different specifications
2545 for release and expiration should be supported by sufficient data to demonstrate that the clinical
2546 performance is not affected, as discussed in the OCH Q1A guidance on stability.

2547 9. Labeling [ICH Q5C]

2548 For most biotechnological/biological drug substances and drug products, precisely defined storage
2549 temperatures are recommended. Specific recommendations should be stated, particularly for drug
2550 substances and drug products that cannot tolerate freezing. These conditions, and where
2551 appropriate, recommendations for protection against light and/or humidity, should appear on
2552 containers, packages, and/or package inserts. Such labeling should be in accordance with section
2553 II.B.11 of this document.

2554 **VIII. CONSIDERATIONS FOR SPECIFIC DOSAGE FORMS**

2555 The following list of parameters for each dosage form is presented as a guide for the types of tests
2556 to be included in a stability study. In general, appearance, assay, and degradation products should
2557 be evaluated for all dosage forms.

2558 The list of tests presented for each dosage form is not intended to be exhaustive, nor is it expected
2559 that every listed test be included in the design of a stability protocol for a particular drug product
2560 (for example, a test for odor should be performed only when necessary and with consideration for
2561 analyst safety). Furthermore, it is not expected that every listed test be performed at each time
2562 point.

2563 **A. Tablets**

2564 Tablets should be evaluated for appearance, color, odor, assay, degradation products, dissolution,
2565 moisture, and friability.

2566 **B. Capsules**

2567 Hard gelatin capsules should be evaluated for appearance (including brittleness), color, odor of
2568 contents, assay, degradation products, dissolution, moisture, and microbial limits.

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2569 Testing of soft gelatin capsules should include appearance, color, odor of content, assay,
2570 degradation products, dissolution, microbial limits, pH, leakage, and pellicle formation. In
2571 addition, the fill medium should be examined for precipitation and cloudiness.

2572 **C. Emulsions**

2573 An evaluation should include appearance (including phase separation), color, odor, assay,
2574 degradation products, pH, viscosity, microbial limits, preservative content, and mean size and
2575 distribution of dispersed phase globules.

2576 **D. Oral Solutions and Suspensions**

2577 The evaluation should include appearance (including formation of precipitate, clarity for solutions),
2578 color, odor, assay, degradation products, pH, preservative content, and microbial limits.

2579 Additionally, for suspensions, redispersibility, rheological properties, and mean size and
2580 distribution of particles should be considered. After storage, samples of suspensions should be
2581 prepared for assay according to the recommended labeling (e.g., shake well before using).

2582 **E. Oral Powders for Reconstitution**

2583 Oral powders should be evaluated for appearance, odor, color, moisture, and reconstitution time.

2584 Reconstituted products (solutions and suspensions) should be evaluated as described in VIII.D.
2585 above, after preparation according to the recommended labeling, through the maximum intended
2586 use period.

2587 **F. Metered-Dose Inhalations and Nasal Aerosols**

2588 Metered-dose inhalations and nasal aerosols should be evaluated for appearance (including
2589 content, container, valve and its components), color, taste, assay, degradation products, assay for
2590 co-solvent (if applicable), dose content uniformity, labeled number of medication actuations per
2591 container meeting dose content uniformity, aerodynamic particle size distribution, microscopic
2592 evaluation, water content, leak rate, microbial limits, valve delivery (shot weight), and
2593 extractables/leachables from plastic and elastomeric components. Samples should be stored in
2594 upright and inverted/on-the-side orientations.

2595 For suspension-type aerosols, the appearance of the valve components and container's contents
2596 should be evaluated microscopically for large particles and changes in morphology of the drug
2597 surface particles, extent of agglomerates, crystal growth, as well as foreign particulate matter.
2598 These particles lead to clogged valves or non-reproducible delivery of a dose. Corrosion of the
2599 inside of the container or deterioration of the gaskets may adversely affect the performance of the
2600 drug product.

2601 A stress temperature cycling study should be performed under the extremes of high and low
2602 temperatures expected to be encountered during shipping and handling to evaluate the effects of

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2603 temperature changes on the quality and performance of the drug product. Such a study may
2604 consist of three or four six-hour cycles per day, between subfreezing temperature and 40°C (75-85
2605 percent RH), for a period of up to six weeks.

2606 Because the inhalant drug products are intended for use in the respiratory system, confirmation
2607 that initial release specifications are maintained should be provided to ensure the absence of
2608 pathogenic organisms (e.g., *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*,
2609 and *Salmonella* species) and that the total aerobic count and total mold and yeast count per
2610 canister are not exceeded.

2611 **G. Inhalation Solutions and Powders**

2612 The evaluation of inhalation solutions and solutions for inhalation should include appearance,
2613 color, assay, degradation products, pH, sterility, particulate matter, preservative and antioxidant
2614 content (if present), net contents (fill weight/volume), weight loss, and extractables/leachables
2615 from plastic, elastomeric and other packaging components.

2616 The evaluation of inhalation powders should include appearance, color, assay, degradation
2617 products, aerodynamic particle size distribution of the emitted dose, microscopic evaluation,
2618 microbial limit, moisture content, foreign particulates, content uniformity of the emitted dose, and
2619 number of medication doses per device meeting content uniformity of the emitted dose (device
2620 metered products).

2621 **H. Nasal Sprays: Solutions and Suspensions**

2622 The stability evaluation of nasal solutions and suspensions equipped with a metering pump should
2623 include appearance, color, clarity, assay, degradation products, preservative and antioxidant
2624 content, microbial limits, pH, particulate matter, unit spray medication content uniformity, number
2625 of actuations meeting unit spray content uniformity per container, droplet and/or particle size
2626 distribution, weight loss, pump delivery, microscopic evaluation (for suspensions), foreign
2627 particulate matter, and extractables/leachables from plastic and elastomeric components of the
2628 container, closure, and pump.

2629 **I. Topical, Ophthalmic and Otic Preparations**

2630 Included in this broad category are ointments, creams, lotions, pastes, gels, solutions, and
2631 nonmetered aerosols for application to the skin.

2632 Topical preparations should be evaluated for appearance, clarity, color, homogeneity, odor, pH,
2633 resuspendability (for lotions), consistency, viscosity, particle size distribution (for suspensions,
2634 when feasible), assay, degradation products, preservative and antioxidant content (if present),
2635 microbial limits/sterility, and weight loss (when appropriate).

2636 Appropriate stability data should be provided for products supplied in closed-end tubes to support
2637 the maximum anticipated use period, during patient use, once the tube seal is punctured allowing
2638 product contact with the cap/cap liner. Ointments, pastes, gels, and creams in large containers,

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2639 including tubes, should be assayed by sampling at the surface, top, middle, and bottom of the
2640 container. In addition, tubes should be sampled near the crimp (see also Section VII.D.2.).

2641 Evaluation of ophthalmic or otic products (e.g., creams, ointments, solutions, and suspensions)
2642 should include the following additional attributes: sterility, particulate matter, and extractables.

2643 Evaluation of nonmetered topical aerosols should include: appearance, assay, degradation
2644 products, pressure, weight loss, net weight dispensed, delivery rate, microbial limits, spray pattern,
2645 water content, and particle size distribution (for suspensions).

2646 **J. Transdermals**

2647 Stability studies for devices applied directly to the skin for the purpose of continuously infusing a
2648 drug substance into the dermis through the epidermis should be examined for appearance, assay,
2649 degradation products, leakage, microbial limit/sterility, peel and adhesive forces, and the drug
2650 release rate.

2651 **K. Suppositories**

2652 Suppositories should be evaluated for appearance, color, assay, degradation products, particle size,
2653 softening range, appearance, dissolution (at 37°C,) and microbial limits.

2654 **L. Small Volume Parenterals (SVPs)**

2655 SVPs include a wide range of injection products such as *Drug Injection*, *Drug for Injection*, *Drug*
2656 *Injectable Suspension*, *Drug for Injectable Suspension*, and *Drug Injectable Emulsion*.

2657 Evaluation of *Drug Injection* products should include appearance, color, assay, preservative
2658 content (if present), degradation products, particulate matter, pH, sterility, and pyrogenicity.

2659 Stability studies for *Drug for Injection* products should include monitoring for appearance, clarity,
2660 color, reconstitution time, and residual moisture content. The stability of *Drug for Injection*
2661 products should also be evaluated after reconstitution according to the recommended labeling.
2662 Specific parameters to be examined at appropriate intervals throughout the maximum intended use
2663 period of the reconstituted drug product, stored under condition(s) recommended in labeling,
2664 should include appearance, clarity, odor, color, pH, assay (potency), preservative (if present),
2665 degradation products/aggregates, sterility, pyrogenicity, and particulate matter.

2666 The stability studies for *Drug Injectable Suspension* and *Drug for Injectable Suspension* products
2667 should also include particle size distribution, redispersibility, and rheological properties in addition
2668 to the parameters cited above for *Drug Injection* and *Drug for Injection* products.

2669 The stability studies for *Drug Injectable Emulsion* products should include, in addition to the
2670 parameters cited above for *Drug Injection*, phase separation, viscosity, and mean size and
2671 distribution of dispersed phase globules.

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2672 The functionality and integrity of parenterals in prefilled syringe delivery systems should be
2673 ensured through the expiration dating period with regard to factors, such as the applied extrusion
2674 force, syringeability, pressure rating, and leakage.

2675 Continued assurance of sterility for all sterile products can be assessed by a variety of means,
2676 including evaluation of the container and closure integrity by appropriate challenge test(s), and/or
2677 sterility testing as described in Section VII.C. Stability studies should evaluate product stability
2678 following exposure to at least the maximum specified process lethality (e.g., F₀, Mrads).

2679 Inclusion of testing for extractables/leachables in the stability protocol may be appropriate in
2680 situations where other qualification tests have not provided sufficient information or assurance
2681 concerning the levels of extractables/leachables from plastics and elastomeric components.

2682 Interaction of administration sets and dispensing devices with parenteral drug products, where
2683 warranted, should also be considered through appropriate use test protocols to assure that
2684 absorption and adsorption during dwell time do not occur.

2685 **M. Large Volume Parenterals (LVPs)**

2686 Evaluation of LVPs should include appearance, color, assay, preservative content (if present),
2687 degradation products, particulate matter, pH, sterility, pyrogenicity, clarity, and volume.

2688 Continued assurance of sterility for all sterile products may be assessed by a variety of means,
2689 including evaluation of the container and closure integrity by appropriate challenge test(s) and/or
2690 sterility testing as described in Section VII.C. Stability studies should include evaluation of
2691 product stability following exposure to at least the maximum specified process lethality (e.g., F₀,
2692 Mrads).

2693 Interaction of administration sets and dispensing devices with this type of dosage form should also
2694 be considered through appropriate use test protocols to ensure that absorption and adsorption
2695 during dwell time do not occur.

2696 **N. Drug Additives**

2697 For any drug product or diluent that is intended for use as an additive to another drug product, the
2698 potential for incompatibility exists. In such cases, the drug product labeled to be administered by
2699 addition to another drug product (e.g., parenterals, inhalation solutions), should be evaluated for
2700 stability and compatibility in admixture with the other drug products or with diluents both in
2701 upright and inverted/on-the-side orientations, if warranted.

2702 A stability protocol should provide for appropriate tests to be conducted at 0-, 6-to-8-, and
2703 24-hour time points, or as appropriate over the intended use period at the recommended
2704 storage/use temperature(s). Tests should include appearance, color, clarity, assay, degradation
2705 products, pH, particulate matter, interaction with the container/closure/device, and sterility.
2706 Appropriate supporting data may be provided in lieu of an evaluation of photodegradation.

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2707 The compatibility and the stability of the drug products should be confirmed in all diluents and
2708 containers and closures as well as in the presence of all other drug products indicated for
2709 admixture in the labeling. Compatibility studies should be conducted on at least the lowest and
2710 highest concentrations of the drug product in each diluent as specified in the labeling. The stability
2711 and compatibility studies should be performed on at least three batches of the drug product.
2712 Compatibility studies should be repeated if the drug product or any of the recommended diluents
2713 or other drug products for admixture are reformulated.

2714 Testing for extractables/leachables on stability studies may be appropriate in situations where other
2715 qualification tests have not provided sufficient information or assurance concerning the levels of
2716 extractables/leachables from plastics and elastomeric components. Interaction of administration
2717 sets and dispensing devices with parenteral drug products, where warranted, should also be
2718 considered through appropriate use test protocols to ensure that absorption and adsorption during
2719 dwell time do not occur.

2720 **O. Implantable Subdermal, Vaginal and Intrauterine Devices that Deliver Drug**
2721 **Products**

2722 A device containing a drug substance reservoir or matrix from which drug substance diffuses
2723 should be tested for total drug substance content, degradation products, extractables, in vitro drug
2724 release rate, and as appropriate, microbial burden or sterility. The stability protocol should include
2725 studies at 37°C or 40°C over a sufficient period of time to simulate the in vivo use of the drug
2726 delivery device.

2727 Stability testing for intrauterine devices (IUDs) should include the following tests: deflection of
2728 horizontal arms or other parts of the frame if it is not a T-shaped device (frame memory), tensile
2729 strength of the withdrawal string, and integrity of the package (i.e., seal strength of the pouch),
2730 and sterility of the device.

2731 **IX. STABILITY TESTING FOR POSTAPPROVAL CHANGES**

2732 **A. General**

2733 Due to the great variety of changes that may be encountered after a drug application is approved, it
2734 is impossible to address stability requirements for all changes in an exhaustive manner in this
2735 guidance. Some more common examples of changes to an approved drug application for which
2736 supportive stability data should be submitted are listed below. All changes should be accompanied
2737 by the standard stability commitment to conduct and/or complete long-term stability studies on the
2738 first 1 or 3 batches of the drug substance and/or drug product and annual batches thereafter, in
2739 accordance with the approved stability protocol. The accumulated stability data should be
2740 submitted in the subsequent annual reports. Unless otherwise noted, if the data give no reason to
2741 believe that the proposed change will alter the stability of the drug product, the previously
2742 approved expiration dating period can be used.

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2743 Historically, all postapproval changes were considered together and required extensive stability
2744 documentation. With the publication of the SUPAC-IR guidance, this approach was changed and
2745 the likelihood of a specific CMC change affecting a drug product’s performance was considered in
2746 creating a multitiered system for evaluating postapproval changes. That system is used in this
2747 guidance. With a higher level change, more stability data will be expected to support that change.
2748 Thus, five stability data package types have been defined, as explained in Table 14.

2749 **Table 14: Stability Data Packages to Support Postapproval Changes**

Stability Data Package	Stability Data at Time of Submission	Stability Commitment
Type 0	None	None beyond the regular annual batches
Type 1	None	First (1) production batch and annual batches thereafter on long-term stability studies.
Type 2	3 months of comparative accelerated data and available long-term data on 1 batch ^a of drug product with the proposed change.	First (1) production batch ^b and annual batches thereafter on long-term stability studies ^c .
Type 3	3 months of comparative accelerated data and available long-term data on 1 batch ^a of drug product with the proposed change.	First 3 production batches ^b and annual batches thereafter on long-term stability studies. ^c
Type 4	3 months of comparative accelerated data and available long-term data on 3 batches ^a of drug product with the proposed change.	First 3 production batches ^b and annual batches thereafter on long-term stability studies. ^c

2757 ^a Pilot scale batches acceptable.

2758 ^b If not submitted in the supplement.

2759 ^c Using the approved stability protocol and reporting data in annual reports.

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2760 The following sections address a number of possible postapproval changes and contain summary
2761 tables with examples of the different levels of change, the stability data package type and, wherever
2762 possible, the filing documentation (AR = annual report; CBE = changes-being-effected
2763 supplement; PA = prior approval supplement) recommended to support each change. The
2764 information presented here is not intended to be exhaustive. Where a specific issue is not covered,
2765 consultation with FDA staff is recommended.

2766 **B. Change in Manufacturing Process of the Drug Substance**

2767 A change in the manufacturing process of the drug substance at the approved manufacturing site
2768 should be supported by the submission of sufficient data to show that such a change does not
2769 compromise the quality, purity, or stability of the drug substance and the resulting drug product.
2770 Because chemical stability of a substance is an intrinsic property, changes made in the preparation
2771 of that substance should not affect its stability, provided the isolated substance remains of
2772 comparable quality for attributes such as particle size distribution, polymorphic form, impurity
2773 profile, and other physiochemical properties. Special concerns for biological products may exist if
2774 changes are made in the manufacturing process of a drug substance that may not exist in a
2775 chemically synthesized drug substance.

2776
2777 Specific submission and stability issues will be addressed in detail in a separate forthcoming
2778 guidance dealing with postapproval changes for drug substances.

2779 **C. Change in Manufacturing Site**

2780 Site changes consist of changes in the location of the site of manufacture, packaging operations,
2781 and/or analytical testing laboratory both of company-owned as well as contract manufacturing
2782 facilities. The stability data package and filing mechanisms indicated below apply to site changes
2783 only. If other changes occur concurrently, the most extensive data package associated with the
2784 individual changes should be submitted.

2785 When a change to a new manufacturer or manufacturing site for any portion of the manufacturing
2786 process of a drug substance or drug product is made, sufficient data to show that such a change
2787 does not alter the characteristics or compromise the quality, purity, or stability of the drug
2788 substance or drug product may be necessary. The data should include a side-by-side comparison
2789 of all attributes to demonstrate comparability and equivalency of the drug substance or drug
2790 product manufactured at the two facilities. New manufacturing locations should have a
2791 satisfactory CGMP inspection.

2792 **1. Site Change for the Drug Substance**

2793 For a change limited to an alternate manufacturing site for the drug substance using similar
2794 equipment and manufacturing process, stability data on the drug substance may not always be
2795 necessary because, for essentially pure drug substances, stability is an intrinsic property of the
2796 material. Biotechnology and biologic products may be an exception (see 21 CFR 601.12 and
2797 314.70 (g)). In general, such a change can be made in a CBE supplement as allowed under 21

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2798 CFR 314.70(c)(3). The standard stability commitment should be made to conduct long-term
2799 stability studies in accordance with the approved stability protocol on the first production batch of
2800 drug product produced from a production batch of drug substance manufactured at the new site.
2801 Ordinarily, the approved expiration dating period for the drug product may be retained if the drug
2802 substance is shown to be of comparable quality (e.g., particle size distribution, polymorphic form,
2803 impurity profile, and other physiochemical properties). If the drug substance is not of comparable
2804 quality, then more extensive stability data on the drug product manufactured from the drug
2805 substance will be needed.

2806 Specific submission and stability issues pertaining to manufacturing site changes for a drug
2807 substance or its intermediates in the drug substance manufacturing process will be addressed in a
2808 separate forthcoming guidance on postapproval changes for the drug substance.

2809 2. Site Change for the Drug Product

2810 For a move of the manufacturing site within an existing facility or a move to a new facility on the
2811 same campus using similar equipment and manufacturing processes, submission of stability data on
2812 the drug product in the new facility prior to implementation is generally not necessary (Table 15).

2813 For a move to a different campus using similar equipment and manufacturing processes, stability
2814 data on the drug product in the new facility should be submitted in a supplemental application.
2815 Three months of accelerated and available long-term stability data on one to three batches of drug
2816 product manufactured in the new site is recommended, depending on the complexity of the dosage
2817 form and the existence of a significant body of information (Table 15). A commitment should be
2818 made to conduct long-term stability studies on the first or first three production batch(es) of the
2819 drug product, depending on the dosage form and the existence of a significant body of information,
2820 manufactured at the new site in accordance with the approved stability protocol. If the stability
2821 data are satisfactory, the existing expiration dating period may be used.

2822 Table 15 reflects the guidance provided in existing SUPAC documents that address the stability
2823 recommendations for the various levels of site change. The stability data package type and filing
2824 mechanisms are as indicated in the table. Note that SUPAC guidances and Table 14 currently do
2825 not apply to biotechnology/biological products (see 21 CFR 314.70(g) and 601.12).

2826 3. Change in Packaging Site for Solid Oral Dosage Form Drug Products

2827 A stand-alone packaging operation site change for solid oral dosage form drug products using
2828 container(s)/closure(s) in the approved application should be submitted as a CBE supplement. No
2829 up-front stability data are necessary. The facility should have a current and satisfactory CGMP
2830 compliance profile for the type of packaging operation under consideration before submitting the
2831 supplement. The supplement should also contain a commitment to place the first production batch
2832 and annual batches thereafter on long-term stability studies using the approved protocol in the
2833 application and to submit the resulting data in annual reports.

2834 A packaging site change for other than solid oral dosage form drug products is considered a
2835 manufacturing site change and the data package that should be submitted for approval is indicated

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2836 in Section IX.C.2.

2837 4. Change in Testing Laboratory

2838 An analytical testing laboratory site change may be submitted as a CBE supplement under certain
 2839 circumstances (see *PAC-ATLS: Postapproval Changes, Analytical Testing Laboratory Sites*, CMC
 2840 10, April 1998). No stability data are required.

2841 **Table 15: Stability Data to Support Postapproval**
 2842 **Drug Product Manufacturing Site Changes^a**

Level of Change	Definition/Examples	Filing Documentation	Stability Data Package
1	a. Manufacturing site change within a facility with the same equipment, SOPs, environmental conditions, controls, personnel (e.g., remodeling an existing building, add-on to an existing facility).	AR	Type 0
	b. Packaging site change for solid oral dosage form drug products.	CBE	Type 1
	c. Test laboratory site change to a new location.	CBE	Type 0
2	Change within a contiguous campus, or between facilities in adjacent city blocks, with the same equipment, SOPs, environmental conditions, controls, personnel: a. <i>Immediate release solid oral and semisolid dosage forms</i>	CBE	Type 1
	b. <i>Modified release dosage forms</i>	CBE	Type 2
3	Manufacturing site change to a different facility with the same equipment, SOPs, environmental conditions, and controls:		<u>SBI^b</u> <u>No SBI^b</u>
	a. <i>Immediate Release Solid Oral Dosage Forms</i>	CBE	Type 2 Type 3
	b. <i>Semisolid Dosage Forms</i>	CBE	Type 3 Type 3
	c. <i>Modified Release Dosage Forms</i>	PA	Type 3 Type 4

2848 ^a Note that metered dose inhalers and dry powder inhalers, transdermal patches, and sterile aqueous solutions are the
 2849 subjects of forthcoming guidances and, except for changes in testing laboratory, are not covered in this table. In
 2850 addition, this table does not apply to biotechnology/biological products.

2851 ^b Significant body of information.

2852

2853 **D. Change in Formulation of the Drug Product**

2854 Historically, all changes in drug product formulation were grouped together and required extensive
2855 stability documentation, usually submitted as a prior-approval supplement. An exception was the
2856 deletion of a color from a product that could be reported in an annual report without supporting
2857 stability data (21 CFR 314.70(d)(4)). Excipients play a critical role in certain complex dosage
2858 forms, including semisolid and modified release drug products. Table 16 provides information on
2859 stability recommendations to support postapproval formulation changes.¹²

¹² Please refer to the following guidance for industry: SUPAC-IR (November 1995), SUPAC-SS (May 1997), and SUPAC-MR (September 1997) for more detailed information on formulation changes for those specific dosage forms.

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Table 16: Stability Data to Support Postapproval Formulation Changes^a

2861
2862

Level of Change	Definition/Examples	Filing Documentation	Stability Data Package				
2863 1	<p>a. <i>All Dosage Forms</i>: Deletion or partial deletion of an ingredient intended to affect the color, taste or fragrance of the drug product.</p> <p>b. <i>Immediate Release Solid Oral and Semisolid Dosage Forms</i>: The total additive effect of all excipient changes does not exceed 5%, with individual changes within the limits specified in SUPAC-IR and -SS.^b</p> <p>c. <i>Semisolid Dosage Forms</i>: Change in supplier of a structure-forming excipient which is primarily a single chemical entity (purity ≥95%).</p> <p>d. <i>Modified Release Dosage Forms</i>: See SUPAC-MR guidance document for specific information on what excipient quantity changes constitute a level 1 change.</p>	AR	Type 1				
2864 2	a. <i>Immediate Release Solid Oral and Semisolid Dosage Forms</i> : The total additive effect of all excipient changes is >5-10% with individual changes within the limits specified in SUPAC-IR and -SS. ^b	PA	Type 2				
	<p>b. <i>Semisolid Dosage Forms</i>: Change in supplier or grade of a structure forming excipient not covered under level 1.</p> <p>c. <i>Semisolid Dosage Forms</i>: Change in the particle size distribution of active drug substance, if the drug is in suspension.</p>	CBE					
	<p>d. <i>Modified Release Dosage Forms</i>: Change in the technical grade and/or specifications of a nonrelease controlling excipient.</p> <p>e. <i>Modified Release Dosage Forms</i>: See SUPAC-MR Guidance document for specific information on what release controlling excipient quantity changes constitute a level 2 change.</p>	PA	see SUPAC-MR				
2865 3	<p>a. <i>All Dosage Forms</i>: Any qualitative or quantitative change in excipient beyond the ranges noted in the level 2 change.</p> <p>b. <i>Semisolid Dosage Forms</i>: Change in the crystalline form of the drug substance, if the drug is in suspension.</p>	PA	<table border="0"> <tr> <td><u>SBI^c</u> Type 2</td> <td><u>No SBI^c</u> Type 3/4</td> </tr> <tr> <td>Type3/4</td> <td>Type 4</td> </tr> </table>	<u>SBI^c</u> Type 2	<u>No SBI^c</u> Type 3/4	Type3/4	Type 4
<u>SBI^c</u> Type 2	<u>No SBI^c</u> Type 3/4						
Type3/4	Type 4						

2866
2867

^a Note that metered dose inhalers and dry powder inhalers, transdermal patches, and sterile aqueous solutions are the subjects of forthcoming guidances and are not covered in this table.

2868
2869
2870

^b Allowable changes in the composition are based on the approved target composition and not on previous Level 1 or level 2 changes in the composition. Changes in diluent (q.s. excipient) due to component and composition changes in excipients are allowed and are excluded from the 10% change limit.

2871

^c Significant body of information.

2872 **E. Addition of a New Strength for the Drug Product**

2873 The addition of a new strength for an approved drug product will generally require the submission
 2874 of a prior-approval supplement. Demonstration of equivalent stability between the approved drug
 2875 product and the new strength will allow extension of the approved drug product expiration dating
 2876 to the new strength. Depending on issues specific to the drug product (e.g., dosage form)
 2877 availability of a significant body of information for the approved dosage form, a Type 2, 3, or 4
 2878 stability data package may be appropriate as shown in Table 17. New strengths intermediate to
 2879 those of an approved drug product may be supported by bracketing/matrixing studies (See Section
 2880 VII.G. and VII.H.).

2881 **Table 17: Stability Data to Support Addition of a New Strength for a Drug Product^a**

Definition of Change	Examples	Filing Documentation	Stability Data Package
New strength of identical qualitative and quantitative composition ^b	a. Addition of a score to an immediate release tablet.	PA	Type 1
	b. Change in the fill of an immediate release hard gelatin capsule.	PA	Type 2
	c. Change in the fill of a hard gelatin capsule containing modified release encapsulated beads.	PA	Type 2
	d. Change in the size of an immediate release tablet or capsule.	PA	Type 3
New strength involving a change in the drug substance to excipient(s) ratio	a. <i>Simple solutions</i> b. <i>Immediate release solid oral dosage forms</i> c. <i>Semisolid and modified release oral dosage forms</i>	PA PA PA	Type 2 Type 3 Type 4

2894 ^a Note that metered dose inhalers and dry powder inhalers, transdermal patches, and sterile aqueous solutions are the
 2895 subjects of forthcoming guidances and are not covered in this table.

2896 ^b No change in drug substance to excipient(s) ratio from the approved drug product.

2897 **F. Change in Manufacturing Process and/or Equipment for the Drug Product**

2898 A change limited to the manufacturing process of the drug product, such as a change in the type of
2899 equipment used, can be supported by the submission of sufficient data to show that such a change
2900 does not alter the characteristics or compromise the stability of the drug product. For information
2901 on determining when equipment is considered to be of the same design and operating principle,
2902 refer to the Supac-IR/MR draft manufacturing equipment addendum (April 1998). In general,
2903 stability data on the drug product demonstrating comparability with and equivalency to the
2904 previously approved drug product should be submitted. The submission types and stability data
2905 packages shown in Table 18 apply to immediate release solid oral dosage forms and semisolid
2906 dosage forms and incorporate the criteria provided by those SUPAC documents. Because
2907 additional data may be appropriate for more complex dosage forms, the chemistry review team
2908 should be consulted. The standard stability commitment to conduct and/or complete the stability
2909 studies on the first three production batches produced by the revised manufacturing process in
2910 accordance with the approved stability protocol is necessary. If the data are found acceptable, the
2911 approved expiration dating period may be retained.

2912 Submissions for approval of a change of manufacturing site for any portion of the manufacturing
2913 process for the drug product are addressed in Section IX.C.

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2914 **Table 18: Stability Data to Support Manufacturing Process Changes^a**

2915 2916 2917 2918	Level of Change	Definition/Examples	Filing Documentation	Stability Data Package	
	2919 1	Process: Changes in processing parameters such as mixing times, operating speeds within application/validation ranges.	AR	Type 0	
		Equipment: Change from nonautomated to automated or mechanical equipment; or Change to alternative equipment of the same design and operating principles.	AR	Type 1	
2920	2	Process: Changes in processing parameters such as mixing times, operating speeds outside of application/validation ranges: a. <i>Immediate release solid oral dosage forms</i> b. <i>Semisolid dosage forms</i> c. <i>Modified release dosage forms</i>	CBE CBE CBE	<u>SBI^b</u> Type 1 Type 2 Type 2	<u>No SBI^b</u> Type 1 Type 4 Type 2
		Equipment: Changes to equipment of different design and/or operating principles: a. <i>Immediate release solid oral dosage forms</i> b. <i>Semisolid dosage forms</i> c. <i>Modified release dosage forms</i>	PA CBE PA	<u>SBI^b</u> Type 2 Type 2 Type 3	<u>No SBI^b</u> Type 3/4 Type 4 Type 4
2921	3	Process: Changes in type of process used in the manufacture of the product, such as a change from wet granulation to direct compression of dry powder: a. <i>Immediate release solid oral dosage forms</i> b. <i>Modified release dosage forms</i>	PA PA	<u>SBI^b</u> Type 2 Type 4	<u>No SBI^b</u> Type 3/4 Type 4

2922 ^a Note that metered dose inhalers and dry powder inhalers, transdermal patches, and sterile aqueous solutions are the
2923 subjects of forthcoming guidances and are not covered in this table. In addition, this table does not apply to
2924 biotechnology/biological products.

2925 ^b Significant body of information.

2926 **G. Change in Batch Size of the Drug Product**

2927 A key question in considering an increase in batch size beyond the production batch size approved
2928 in the application is whether the change involves a change in equipment or its mode of operation,
2929 or other manufacturing parameters described for the approved batch size. If no equipment change
2930 is planned, then the next concern is the size of the change relative to the approved batch size, with
2931 larger changes expected to present a greater risk of stability problems in the drug product. Table
2932 19 presents the recommended stability data packages for a variety of batch size situations not
2933 involving equipment or mode of operation changes.

2934 If an equipment change is part of the batch size change, please refer to Change in Manufacturing
2935 Process of the Drug Product (Section IX.F.).

2936 **Table 19: Stability Data to Support Postapproval Batch Size Changes^a**

2937 2938	Level of Change	Definition/Examples	Filing Documentation	Stability Data Package
2939	1	<i>Solid oral dosage forms</i> (i.e., tablets, capsules, powders for reconstitution), <i>semisolid dosage forms</i> , and <i>oral solutions</i> : A change in batch size up to and including a factor of ten times the size of the pivotal clinical trial/biobatch.	AR	Type 1
2940	2	<i>Solid oral dosage forms</i> (i.e., tablets, capsules, powders for reconstitution), <i>semisolid dosage forms</i> , and <i>oral solutions</i> : A change in batch size beyond a factor of ten times the size of the pivotal clinical trial/biobatch.	CBE	Type 2

2941 ^a Note that metered dose inhalers and dry powder inhalers, transdermal patches, and sterile aqueous solutions are the
2942 subjects of forthcoming guidances and are not covered in this table.

2943

2944 **H. Reprocessing of a Drug Product**

2945 Stability data submitted in support of reprocessing of a specific batch of a drug product should
2946 take into account the nature of the reprocessing procedure and any specific impact that might have
2947 upon the existing stability profile of the drug. The expiration dating period for a reprocessed batch
2948 should not exceed that of the parent batch, and the expiration date should be calculated from the
2949 original date of manufacture of the oldest batch.

2950 The acceptability of reprocessing of a specific batch of a drug product will depend on the nature of
2951 the reprocessing procedure, which can range from repackaging a batch when packing equipment
2952 malfunctions to regrinding and recompressing tablets. The appropriate chemistry review team
2953 should be contacted to determine whether or not the reprocessing procedure is acceptable. Any
2954 batch of the drug product that is reprocessed should be placed on accelerated and long-term
2955 stability studies using the approved protocol to generate a Type 2 stability data package.

2956 **I. Change in Container and Closure of the Drug Product**

2957 The stability data packages for changes in container and closure of a drug product vary (Table 20).
2958 The first factor used in determining the stability data package recommendation is whether or not
2959 the protective properties of the container/closure system are affected by the proposed change.
2960 Protective properties of the container/closure system include, but are not limited to, moisture
2961 permeability, oxygen permeability, and light transmission. Changes that may affect these
2962 properties should be supported by a greater amount of data to support the change. The second
2963 factor is the nature of the dosage form itself. A solid dosage form will generally be less affected by
2964 a container change than a liquid dosage form. Because considerably more information will be
2965 needed to document a container/closure change than just stability data, applicants are encouraged
2966 to consult with the appropriate chemistry review team to determine the appropriate filing
2967 mechanisms. Please refer to the guidance for industry: *Submission of Documentation in Drug*
2968 *Applications for Container Closure Systems Used for the Packaging of Human Drugs and*
2969 *Biologics* for qualification and quality control information requested for container closure
2970 systems.¹³ Table 20 below describes what type of stability data should be supplied for some of the
2971 most common post-approval changes to container/closure systems for solid and liquid oral drug
2972 products.

¹³A forthcoming guidance will deal more extensively with postapproval packaging changes for all dosage forms.

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Table 20: Stability Data to Support Postapproval Container/Closure Changes for Solid and Liquid Oral Drug Products^a

Type of change	Definition	Examples	Stability Data Package
Changes that do not affect the protective properties of the container/closure system	1. Closure changes	Adding or changing a child-resistant feature to a packaging system or changing from a metal to a plastic screw cap, while the inner seal remains unchanged.	Type 0
	2. Changing the secondary packaging	Changing a carton.	Type 0
	3. Removal of non-drug product material	Removing: a. an insert. b. a filler.	Type 0 Type 1
	4. Changing shape of container/closure	(Without changing the size)	Type 0
	5. Changing size of container/closure	a. Within the approved range of sizes. b. Outside the approved range of sizes.	Type 0 Type 2
Changes that may affect the protective properties of the container/closure system	1. Adding or changing a component to increase protection within the same system.	a. Adding, or changing to, a heat-induction seal: i. For a solid oral drug product. ii. For a liquid oral drug product. b. Adding or changing a desiccant or a filler. c. Adding an overwrap or carton.	Type 1 Type 2 Type 2 Type 2
	2. Changing the manufacturer or formulation of a container/closure component, including bottle or blister resin, cap liner, seal laminate, desiccant, filler, etc., within the same system.	a. Using an approved or compendial container or closure equivalency protocol for: i. a solid oral drug product. ii. a liquid oral drug product. b. Without an approved or compendial container or closure equivalency protocol.	Type 1 Type 1 Type 2
	3. Changing to a different container and closure system	For any solid or liquid oral drug product.	<u>SBI^b</u> Type 3 <u>No SBI^b</u> Type 4

^a In certain situations, e.g., for particularly sensitive drug products, additional stability requirements may apply. Note that Metered Dose Inhalers and Dry Powder Inhalers, Transdermal Patches, and Sterile Aqueous Solutions are the subject of a forthcoming guidance and are not covered in this table.

^b Significant body of information.

2992 **J. Changes in the Stability Protocol**

2993 In general, modification of the approved stability protocol is discouraged until the expiration dating
2994 period granted at the time of approval has been confirmed by long-term data from production
2995 batches. However, changes in analytical methods provide increased assurance in product identity,
2996 strength, quality, and purity, or to comply with USP monographs, may be appropriate prior to the
2997 confirmation of the expiration dating period.

2998 Certain parameters may be reduced in test frequency or omitted from the stability protocol for annual
2999 batches on a case-by-case basis through a prior-approval supplement. A justification for such a
3000 reduction or omission should be adequately provided.

3001 If justified, test frequency for all parameters may be reduced for *annual batches* based on
3002 accumulated stability data. Such a modification to the approved stability protocol should be
3003 submitted as a prior-approval supplement. The justification may include a demonstrated history of
3004 satisfactory product stability, which may in turn include, but not be limited to, full long-term stability
3005 data from at least three production batches. The reduced testing protocol should include a minimum
3006 of four data points, including the initial time point, and the expiry and two points in between. For
3007 example, drug products with an expiration dating period of less than 18 months should be tested at
3008 quarterly intervals; products with an expiration dating period of 18 but not more than 30 months
3009 should be tested semiannually; and products with an expiration dating period of 36 months or longer
3010 should be tested annually. It should be noted, however, that the reduced testing protocol applies
3011 only to annual batches and does not apply to batches used to support a postapproval change that
3012 requires long-term stability data at submission and/or as a commitment. Furthermore, whenever
3013 product stability failures occur, the original full protocol should be reinstated for annual batches until
3014 problems are corrected.

3015 A bracketing or matrixing design, if proposed for annual batches or to support a supplemental
3016 change, should be submitted as a prior-approval supplement (see Sections VII.G. and H.). It is
3017 acceptable to submit these modifications to the protocol, along with data generated therefrom to
3018 support a supplemental change, in one combined prior-approval supplement. However, the applicant
3019 is encouraged to consult with the appropriate FDA chemistry review team before initiating such
3020 studies.

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3061

GLOSSARY

3062 **Accelerated Testing [ICH Q1A]**

3063 Studies designed to increase the rate of chemical degradation or physical change of an active drug
3064 substance and drug product by using exaggerated storage conditions as part of the formal, definitive,
3065 stability protocol. These data, in addition to long-term stability data, may also be used to assess
3066 longer term chemical effects at nonaccelerated conditions and to evaluate the impact of short-term
3067 excursions outside the label storage conditions such as might occur during shipping. Results from
3068 accelerated testing studies are not always predictive of physical changes.

3069 **Acceptance Criteria [21 CFR 210.3]**

3070 Product specifications and acceptance/rejection criteria, such as acceptable quality level and
3071 unacceptable quality level, with an associated sampling plan, that are necessary for making a decision
3072 to accept or reject a lot or batch (or any other convenient subgroups of manufactured units).

3073 **Active Substance; Active Ingredient; Drug Substance; Medicinal Substance [ICH Q1A]**

3074 The unformulated drug substance which may be subsequently formulated with excipients to produce
3075 the drug product.

3076 **Approved Stability Protocol**

3077 The detailed study plan described in an approved application to evaluate the physical, chemical,
3078 biological, and microbiological characteristics of a drug substance and a drug product as a function
3079 of time. The approved protocol is applied to generate and analyze acceptable stability data in
3080 support of the expiration dating period. It may also be used in developing similar data to support an
3081 extension of that expiration dating period, and other changes to the application. It should be
3082 designed in accordance with the objectives of this guidance.

3083 **Batch [21 CFR 210.3(b)(2)]**

3084 A specific quantity of a drug material that is intended to have uniform character and quality, within
3085 specified limits, and is produced according to a single manufacturing order during the same cycle of
3086 manufacture.

3087 **Bracketing [ICH Q1A]**

3088 The design of a stability schedule so that at any time point only the samples on the extremes, for
3089 example, of container size and/or dosage strengths, are tested. The design assumes that the stability
3090 of the intermediate condition samples is represented by those at the extremes.
3091

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3092 **Climatic Zones** [ICH Q1A]

3093 The concept of dividing the world into four zones based on defining the prevalent annual climatic
3094 conditions.

3095 **Complex Dosage Form**

3096 A complex dosage form is one where quality and/or stability is more likely to be affected by changes
3097 because the release mechanism, delivery system, and manufacturing process are more complicated
3098 and thus more susceptible to variability.

3099 Examples of complex dosage forms include modified-release dosage forms, metered-dose inhalers,
3100 transdermal patches, liposome preparations. Due to the diversity of currently marketed dosage forms
3101 and the ever-increasing complexity of new delivery systems, it is impossible to clearly identify simple
3102 vs. complex dosage forms in an exhaustive manner. Applicants are advised to consult with the
3103 appropriate FDA chemistry review team when questions arise.

3104 **Conjugated Product** [ICH Q5C]

3105 A conjugated product is made up of an active ingredient (e.g., peptide, carbohydrate) bound
3106 covalently or noncovalently to a carrier (e.g., protein, peptide, inorganic mineral) with the objective
3107 of improving the efficacy or stability of the product.

3108 **Confirmatory Studies** [ICH Q1B]

3109 Those studies undertaken to establish photostability characteristics under standardized conditions.
3110 These studies are used to identify precautionary measures needed in manufacturing or formulation
3111 and whether light-resistant packaging and/or special labeling is needed to mitigate exposure to light.
3112 For the confirmatory studies, the batch(es) should be selected according to batch selection for
3113 long-term and accelerated testing which is described in the parent guidance.

3114 **Controlled Room Temperature (CRT)** [USP]

3115 A temperature maintained thermostatically that encompasses the usual and customary working
3116 environment of 20°C to 25°C (68°F to 77°F) that results in a mean kinetic temperature (MKT)
3117 calculated to be not more than 25°C and that allows for excursions between 15°C and 30°C (59°F
3118 to 86°F) that are experienced in pharmacies, hospitals and warehouses.

3119 **Date of Production**

3120 The date that the first step of manufacture is performed which involves the combining of an active
3121 ingredient, antioxidant, or preservative, with other ingredients in the production of a dosage form.
3122 For drug products consisting of a single ingredient filled into a container, the date of the production
3123 is the initial date of the filling operation. For a biological product subject to licensure see the
3124 definition of date of manufacture in 21 CFR 610.50.

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3125 **Degradation Product** [ICH Q5C]

3126 A molecule resulting from a change in the drug substance bulk material) brought about over time.
3127 For the purpose of stability testing of the products described in this guidance, such changes could
3128 occur as a result of processing or storage (e.g., by deamidation, oxidation, aggregation, proteolysis).
3129 For biotechnological/biological products, some degradation products may be active.

3130 **Dosage Form; Preparation** [ICH Q1A]

3131 A pharmaceutical product type, for example tablet, capsule, solution, cream, that contains a drug
3132 substance, generally, but not necessarily, in association with excipients.

3133 **Drug Product; Finished Product** [ICH Q1A]

3134 The dosage form in the final immediate packaging intended for marketing.

3135 **Drug Substance; Active Substance** [21 CFR 312.3(b)]

3136 An active ingredient that is intended to furnish pharmacological activity or other direct effect in the
3137 diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any
3138 function of the human body.

3139 **Excipient** [ICH Q1A]

3140 Anything other than the drug substance in the dosage form.

3141 **Expiry/Expiration Date** [ICH Q1A]

3142 The date placed on the container/labels of a drug product designating the time during which a batch
3143 of the product is expected to remain within the approved shelf-life specification if stored under
3144 defined conditions, and after which it must not be used.

3145 **Extractables/Leachables**

3146 Materials or components derived from the container/closure which have been transferred into the
3147 contained drug substance or drug product.

3148 **Forced Degradation Testing Studies** [ICH Q1B]

3149 Those studies undertaken to degrade the sample deliberately. These studies, which may be
3150 undertaken in the development phase normally on the drug substances, are used to evaluate the
3151 overall photosensitivity of the material for method development purposes and/or degradation
3152 pathway elucidation.

3153 **Formal (Systematic) Studies** [ICH Q1A]

3154 Formal studies are those undertaken to a preapproval stability protocol which embraces the

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3155 principles of these guidances.

3156 **Immediate (Primary) Pack** [ICH Q1B]

3157 That constituent of the packaging that is in direct contact with the drug substance or drug product,
3158 and includes any appropriate label.

3159 **Impurity**

3160 Any entity of the drug substance (bulk material) or drug product (final container product) that is not
3161 the chemical entity defined as the drug substance, an excipient, or other additives to the drug
3162 product.

3163 **Intermediate** [ICH Q5C]

3164 For biotechnological/biological products, a material produced during a manufacturing process that is
3165 not the drug substance or the drug product but for which manufacture is critical to the successful
3166 production of the drug substance or the drug product. Generally, an intermediate will be quantifiable
3167 and specifications will be established to determine the successful completion of the manufacturing
3168 step before continuation of the manufacturing process. This includes material that may undergo
3169 further molecular modification or be held for an extended period before further processing.

3170 **Long-Term (Real-Time) Testing** [ICH Q1A]

3171 Stability evaluation of the physical, chemical, biological, and microbiological characteristics of a drug
3172 product and a drug substance, covering the expected duration of the shelf life and retest period,
3173 which are claimed in the submission and will appear on the labeling.

3174 **Lot** [21 CFR 210.3(b)(10)]

3175 A batch, or a specific identified portion of a batch, having uniform character and quality within
3176 specified limits; or, in the case of a drug product produced by continuous process, it is a specific
3177 identified amount produced in a unit of time or quantity in a manner that assures its having uniform
3178 character and quality within specific limits.

3179 **Manufacturing-Scale Production** [ICH Q5C]

3180 Manufacture at the scale typically encountered in a facility intended for product production for
3181 marketing.

3182 **Marketing Pack** [ICH Q1B]

3183 The combination of immediate pack and other secondary packaging such as a carton.

3184 **Mass Balance (Material Balance)** [ICH Q1A]

3185 The process of adding together the assay value and levels of degradation products to see how closely

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3186 these add up to 100 per cent of the initial value, with due consideration of the margin of analytical
3187 precision.

3188 This concept is a useful scientific guide for evaluating data but it is not achievable in all
3189 circumstances. The focus may instead be on assuring the specificity of the assay, the completeness of
3190 the investigation of routes of degradation, and the use, if necessary, of identified degradants as
3191 indicators of the extent of degradation via particular mechanisms.

3192 **Matrixing** [ICH Q1A]

3193 The statistical design of a stability schedule so that only a fraction of the total number of samples are
3194 tested at any specified sampling point. At a subsequent sampling point, different sets of samples of
3195 the total number would be tested. The design assumes that the stability of the samples tested
3196 represents the stability of all samples. The differences in the samples for the same drug product
3197 should be identified as, for example, covering different batches, different strengths, different sizes of
3198 the same container and closure, and, possibly, in some cases different containers/closure systems.

3199 Matrixing can cover reduced testing when more than one variable is being evaluated. Thus the
3200 design of the matrix will be dictated by the factors needing to be covered and evaluated. This
3201 potential complexity precludes inclusion of specific details and examples, and it may be desirable to
3202 discuss design in advance with the FDA chemistry review team where this is possible. In every case,
3203 it is essential that all batches are tested initially and at the end of the long-term testing period.

3204 **Mean Kinetic Temperature** [ICH Q1A]

3205 Mean kinetic temperature (MKT)¹⁴ is defined as the isothermal temperature that corresponds to the
3206 kinetic effects of a time-temperature distribution.

3207 **Modified Release Dosage Forms** [SUPAC-MR]

3208 Dosage forms whose drug-release characteristics of time course and/or location are chosen to
3209 accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as a
3210 solution or an immediate release dosage form. Modified release solid oral dosage forms include both
3211 delayed and extended release drug products.

3212 **New Dosage Form** [ICH Q1C]

3213 A drug product which is a different pharmaceutical product type, but contains the same active
3214 substance as included in the existing drug product approved by the pertinent regulatory authority.

3215 **New Molecular Entity; New Active Substance** [ICH Q1A]

3216 A substance which has not previously been registered as a new drug substance with the national or

¹⁴ J.D. Haynes, "Worldwide Virtual Temperatures for Product Stability Testing", *J. Pharm. Sci.*, Vol. 60, No. 6, 927 (June 1971).

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3217 regional authority concerned.

3218 **Pilot-Plant Scale**

3219 The manufacture of either drug substance or drug product by a procedure fully representative of and
3220 simulating that to be applied on a full manufacturing scale.

3221 For oral solid dosage forms this is generally taken to be at a minimum scale of one tenth that of full
3222 production or 100,000 tablets or capsules, whichever is the larger. [Q1A]

3223 For biotechnology products, the methods of cell expansion, harvest, and product purification should
3224 be identical except for the scale of production.
3225 [ICH Q5C]

3226 **Primary Stability Data** [ICH Q1A]

3227 Data on the drug substance stored in the proposed packaging under storage conditions that support
3228 the proposed retest date.

3229 Data on the drug product stored in the proposed container/closure for marketing under storage
3230 conditions that support the proposed shelf life.

3231 **Production Batch**

3232 A batch of a drug substance or drug product manufactured at the scale typically encountered in a
3233 facility intended for marketing production.

3234 **Random Sample**

3235 A selection of units chosen from a larger population of such units so that the probability of inclusion
3236 of any given unit in the sample is defined. In a simple random sample, each unit has equal chance of
3237 being included. Random samples are usually chosen with the aid of tables of random numbers found
3238 in many statistical texts.

3239 **Reference Listed Drug** [21 CFR 314.3]

3240 The listed drug identified by FDA as the drug product upon which an applicant relies in seeking
3241 approval of its abbreviated application.

3242 **Retest Date** [ICH Q1A]

3243 The date when samples of the drug substance should be reexamined to ensure that the material is still
3244 suitable for use.

3245 **Retest Period** [ICH Q1A]

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3246 The time interval during which the drug substance can be considered to remain within the
3247 specifications and therefore acceptable for use in the manufacture of a given drug product, provided
3248 that it has been stored under the defined conditions; after this period the batch should be retested for
3249 compliance with specifications and then used immediately.

3250 Semi-Permeable Container

3251 A container which permits the passage of a solvent, such as water contained therein, but prevents the
3252 passage of the dissolved substance or solute, thus resulting in an increased concentration of the latter
3253 over time. It may also permit the ingress of foreign volatile materials. The transport of the solvent,
3254 its vapor, or other volatile material occurs through the container by dissolution into one surface,
3255 diffusion through the bulk of the material, and desorption from the other surface, all caused by a
3256 partial-pressure gradient. Examples of semi-permeable containers include plastic bags or semi-rigid
3257 LDPE for LVPs, and LDPE ampoules, vials, or bottles for inhalation or ophthalmic solutions.

3258 Semisolid Dosage Forms [SUPAC-SS]

3259 Semi-solid dosage forms include non-sterile and semi-solid preparations, e.g., creams, gels and
3260 ointments, intended for all topical routes of administration.

3261 Shelf Life; Expiration Dating Period [ICH Q1A]

3262 The time interval that a drug product is expected to remain within the approved shelf-life
3263 specification provided that it is stored under the conditions defined on the label in the proposed
3264 containers and closure.

3265 Significant Body of Information [SUPAC-IR/MR]

3266

3267 Immediate Release Solid Oral Dosage Forms

3268 A significant body of information on the stability of the drug product is likely to exist after five years
3269 of commercial experience for new molecular entities, or three years of commercial experience for
3270 new dosage forms.

3271 Modified Release Solid Oral Dosage Forms

3272

3273 A significant body of information should include, for “Modified Release Solid Oral Dosage Forms,” a
3274 product-specific body of information. This product-specific body of information is likely to exist
3275 after five years of commercial experience for the original complex dosage form drug product, or
3276 three years of commercial experience for any subsequent complex dosage form drug product.

3277 Significant Change [ICH Q1A]

3278 Significant change for a drug product at the accelerated stability condition and the intermediate
3279 stability condition is defined as:

3280 1. A 5 percent potency loss from the initial assay value of a batch;

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- 3281 2. Any specified degradant exceeding its specification limit;
3282 3. The product exceeding its pH limits;
3283 4. Dissolution exceeding the specification limits for 12 capsules or tablets;
3284 5. Failure to meet specifications for appearance and physical properties, e.g., color, phase
3285 separation, resuspendibility, delivery per actuation, caking, hardness.

3286 **Simple Dosage Form**

3287 A dosage form whose quality and/or stability is less likely to be affected by the manufacturing site
3288 because the release mechanism, delivery system, and manufacturing process are less complicated and
3289 less susceptible to variability.

3290 Examples of simple dosage forms include immediate-release solid oral dosage forms, e.g., tablets,
3291 capsules, semi-solid dosage forms, and oral and parenteral solutions. Due to the diversity of
3292 currently marketed dosage forms and the ever-increasing complexity of new delivery systems, it is
3293 impossible to clearly identify simple vs. complex dosage forms in an exhaustive manner. Applicants
3294 are advised to consult with the appropriate FDA chemistry review team when questions arise.

3295 **Site-Specific Batches**

3296 Batches of drug substance or drug product made at the intended manufacturing scale production site
3297 from which stability data are generated to support the approval of that site, as well as to support the
3298 proposed retest period or expiration dating period, respectively, in an application. The site-specific
3299 batch(es) of the drug product should be made from identifiable site-specific batch(es) of the drug
3300 substance whenever possible.

3301 **Specification-Check/Shelf-life [ICH Q1A]**

3302 The combination of physical, chemical, biological and microbiological test requirements that a drug
3303 substance must meet up to its retest date or a drug product must meet throughout its shelf life.

3304 **Specification-Release [ICH Q1A]**

3305 The combination of physical, chemical, biological and microbiological test requirements that
3306 determine that a drug product is suitable for release at the time of its manufacture.

3307 **Stability**

3308 The capacity of a drug substance or a drug product to remain within specifications established to
3309 ensure its identity, strength, quality, and purity throughout the retest period or expiration dating
3310 period, as appropriate.

3311 **Stability Commitment**

3312 A statement by an applicant to conduct and/or complete prescribed studies on production batches of
3313 a drug product after approval of an application.

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3314 **Stability-Indicating Methodology**

3315 Validated quantitative analytical methods that can detect the changes with time in the chemical,
3316 physical, or microbiological properties of the drug substance and drug product, and that are specific
3317 so that the contents of active ingredient, degradation products, and other components of interest can
3318 be accurately measured without interference.

3319 **Stability Profile**

3320 The physical, chemical, biological, and microbiological behavior of a drug substance or drug product
3321 as a function of time when stored under the conditions of the Approved Stability Protocol.

3322 **Storage Conditions Tolerances** [ICH Q1A]

3323 The acceptable variation in temperature and relative humidity of stability storage.

3324 **Strength** [21 CFR 210.3(b)(16)]

3325 The concentration of the drug substance (for example weight/weight, weight/volume, or unit
3326 dose/volume basis), and/or the potency, that is, the therapeutic activity of the drug product as
3327 indicated by appropriate laboratory test or by adequately developed and controlled clinical data
3328 (expressed for example, in terms of units by reference to a standard).

3329 **Stress Testing - Drug Substance** [ICH Q1A]

3330

3331 Studies undertaken to elucidate intrinsic stability characteristics. Such testing is part of the
3332 development strategy and is normally carried out under more severe conditions than those used for
3333 accelerated tests.

3334 **Stress Testing - Drug Product** [ICH Q1A]

3335 Light testing should be an integral part of stress testing.

3336 Special test conditions for specific products (e.g., metered dose inhalations and creams and
3337 emulsions) may require additional stress studies.

3338 **Supporting Stability Data** [ICH Q1A]

3339 Data other than the primary stability data, such as stability data on early synthetic route batches of
3340 drug substance, small scale batches of materials, investigational formulations not proposed for
3341 marketing, related formulations, product presented in containers and/or closures other than those
3342 proposed for marketing, information regarding test results on containers, and other scientific
3343 rationale that support to the analytical procedures, the proposed retest period or shelf life and
3344 storage conditions.

3345 **Tentative Expiration Dating Period**

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3346 A provisional expiration dating period which is based on acceptable accelerated data, statistical
3347 analysis of available long-term data, and other supportive data for an NDA product, or on acceptable
3348 accelerated data for an ANDA product, but not on full long-term stability data from at least three
3349 production batches.