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Mr. Devinder Gill
Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Reference: Docket No. 2005D-0312

Dear Mr. Devinder:

I appreciate the opportunity for comments on the subject document. Attached you will find my comments and questions pertaining the subject document. They are highlighted in red, within the document. Should you need anything else, feel free to contact me at your convenience.

Cordially,

Angel L. Rodriguez, RAC
Regulatory Affairs Director
KV Pharmaceutical Company
Ph: 314-645-6600
Fx: 314-567-0704
e-mail: arodriguez@kvph.com

2005D-0312

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Guidance for Industry
ANDAs: Impurities in Drug Products

5 *This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's)*
6 *current thinking on this topic. It does not create or confer any rights for or on any person and does*
7 *not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies*
8 *the requirements of the applicable statutes and regulations. If you want to discuss an alternate*
9 *approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call*
10 *the appropriate number listed on the title page of this document.*

11
12 *If you plan to submit comments on this draft guidance, to expedite FDA review of your comments,*
13 *please:*

- 14
15
 - *Clearly explain each issue/concern and, when appropriate, include a proposed revision*
16 *and the rationale and/or justification for the proposed revision.*
 - *Identify specific comments by line numbers; use the pdf version of the document*
17 *whenever possible.*
 - *If possible, e-mail an electronic copy (Word) of the comments you have submitted to the*
18 *docket to cummingsd@cderr.fda.gov.*

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22 **I. INTRODUCTION**

23
24 This guidance provides recommendations on what chemistry, manufacturing and controls (CMC)
25 information sponsors should include regarding the reporting, identification, and qualification of
26 impurities that are classified as *degradation products* in drug products when submitting:^{1,2}

- 27
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 - Original abbreviated new drug applications (ANDAs)
 - ANDA supplements for changes that may affect the quantitative or qualitative
29 degradation product profile

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33 The guidance also provides recommendations for establishing acceptance criteria for degradation
34 products (specifically, degradation products of the active ingredient or reaction products of the
35 active ingredient with an excipient(s) and/or immediate container/closure system) in generic drug
36 products. The guidance will replace an existing 1998 draft guidance of the same name.

37
38 This guidance does not apply to an ANDA or ANDA supplement that has been reviewed prior to
39 the publication of the final guidance.
40

¹ The recommendations in this guidance are limited to drug products that are manufactured from drug substances produced by chemical synthesis.

² See 21 CFR 314.94(a)(9)

41 FDA's guidance documents, including this guidance, do not establish legally enforceable
42 responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should
43 be viewed only as recommendations, unless specific regulatory or statutory requirements are
44 cited. The use of the word *should* in Agency guidances means that something is suggested or
45 recommended, but not required.
46

47 II. BACKGROUND

48
49 We are revising the draft guidance for industry titled *ANDAs: Impurities in Drug Products*,
50 issued in December 1998, for the following reasons:
51

- 52 1. To update information on listing of degradation products, setting acceptance criteria,
53 and qualifying degradation products (thresholds and procedures) in ANDAs in
54 conformance with the revision of the guidance for industry (November 2003) on
55 *Q3B(R) Impurities in New Drug Products*.
56
- 57 2. To remove those sections of the 1998 draft guidance containing recommendations
58 that are no longer needed because they are addressed in the more recent *Q3B(R)* (see
59 the list below).
60

61 The *Q3B(R)* was developed by the International Conference on Harmonisation (ICH) to provide
62 guidance on impurities in drug products for new drug applications (NDAs). However, the
63 Agency believes that many of the recommendations provided on impurities in drug products also
64 apply to ANDAs. Please refer to the following specific sections in the *Q3B(R)* for these
65 recommendations:
66

- 67 • Section I, Introduction
- 68 • Section II, Rationale for the Reporting and Control of Degradation Products
- 69 • Section III, Analytical Procedures
- 70 • Section IV, Reporting Degradation Products, Content of Batches
- 71 • Attachment 1, Thresholds for Degradation Products
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73

74 III. LISTING OF DEGRADATION PRODUCTS AND SETTING ACCEPTANCE 75 CRITERIA FOR DEGRADATION PRODUCTS IN DRUG PRODUCT 76 SPECIFICATIONS 77

78 A. Listing of Degradation Products 79

80 We recommend that the specification for a drug product include a list of degradation products.
81 Stability studies, chemical development studies, and routine batch analyses can be used to
82 predict the degradation profile for the commercial product. It is important that the list of
83 degradation products for the drug product specification be based on degradation products found
84 in the batch(es) manufactured by the proposed commercial process. This statement appears to
85 negate the validity of data generated from experimental batches manufactured following the

*Contains Nonbinding Recommendations
Draft — Not for Implementation*

86 scheme of the proposed commercial process but not manufactured in production equipment. In
87 the development of specifications for generic drug products, the use of all available data
88 (experimental and pivotal) is paramount. Further, in cases where the proposed product formula
89 is the same as that of the reference listed drug product, the use of stability data from the
90 reference listed drug product should also be allowed. Many times you see greater levels of
91 degradants in RLDs than in the proposed product. However, this difference in degradant levels
92 may exist due to process or raw material variables that the manufacturer of the proposed product
93 has not encounter yet. If the ANDA applicant demonstrates that the RLD has certain levels of
94 degradants, FDA should approve specifications for the proposed product based on the RLD
95 levels, regardless of the levels found in the proposed product.

96 We recommend that you include in your submission a rationale for the inclusion or exclusion of
97 degradation products in the drug product specification. It is important that the rationale include a
98 discussion of the degradation profiles observed in stability studies and in the degradation profiles
99 observed in the batch(es) under consideration together with a consideration of the degradation
100 profile of the batch(es) manufactured by the proposed commercial process. Structural analysis of
101 potential degradants can also be used to justify the inclusion or exclusion of degradation products
102 in the drug product specification. Many times the conditions through which a degradant is
103 produce are non-existent in the proposed product.

104 Individual degradation products with specific acceptance criteria that are included in the
105 specification for the drug product are referred to as "*specified degradation products*" in this
106 guidance. Specified degradation products can be *identified* or *unidentified*. *Could you please*
107 *elaborate on the meaning of a "specified unidentified degradation product? It seems a*
108 *degradant falls under a known impurity or a "specified degradation product". Anything else*
109 *falls under unknown impurities. Thus the meaning of "specified unidentified degradation*
110 *product" is somewhat obscure.*

111 We recommend that specified identified degradation products be included in the list of
112 degradation products along with specified unidentified degradation products that are estimated to
113 be present at a level greater than the identification threshold given in Q3B(R). For degradation
114 products known to be unusually potent or to produce toxic or unexpected pharmacological
115 effects, we recommend that the quantitation and/or detection limit of the analytical procedures
116 correspond to the level at which the degradation products are expected to be controlled.

117 For unidentified degradation products to be listed in the drug product specification, we
118 recommend that you clearly state the procedure used and assumptions made in establishing the
119 level of the degradation product. It is important that *specified unidentified* degradation products
120 be referred to by an appropriate qualitative analytical descriptive label (e.g., unidentified A,
121 unidentified with relative retention of 0.9). We recommend that you also include general
122 acceptance criteria of not more than the identification threshold (see *Q3B(R)*, Attachment 1) for
123 any unspecified degradation product and acceptance criteria for total degradation products.

124 We recommend that the drug product specification include, where applicable, a list of the
125 following types of degradation products:

- 126 • Each specified identified degradation product
- 127 • Each specified unidentified degradation product

- 128 • Any unspecified degradation product with an acceptance criterion of not more than (\leq)
129 the figure in the identification threshold in Attachment 1, Q3B(R)
130 • Total degradation products. In the past, FDA has requested specifications for Total
131 Known, Total Unknown, and Total Impurities (Known + Unknown). Is FDA's proposal
132 to do away with the current classification and place one single specification for Total
133 Degradation Products?

134
135 **B. Setting Acceptance Criteria for Degradation Products**
136

137 We recommend that the acceptance criterion be set no higher than the qualified level (see section
138 IV, Qualification of Degradation Products). In establishing degradation product acceptance
139 criteria, the first critical consideration is whether a degradation product is specified in the United
140 States Pharmacopeia (USP). If there is a monograph in the USP that includes a limit for a
141 specified identified degradation product, we recommend that the acceptance criterion be set no
142 higher than the official compendial limit.

143
144 If the level of the degradation product is above the level specified in the USP, we recommend
145 qualification. Then, if appropriate qualification has been achieved, an applicant may wish to
146 petition the USP for revision of the degradation product's acceptance criterion.

147
148 If the acceptance criterion for a specified degradation product does not exist in the USP and this
149 degradation product can be qualified by comparison to an FDA-approved human drug product,
150 the acceptance criterion should be consistent with the level observed in the approved human drug
151 product. In other circumstances, the acceptance criterion may need to be set lower than the
152 qualified level to ensure drug product quality. For example, if the level of the metabolite
153 impurity is too high, other quality attributes, like potency, could be seriously affected. For this to
154 happen, FDA must be required to have specific data that demonstrates that an active metabolite
155 has lower pharmacologic activity than the API. For example, if bioequivalence is determined by
156 analysis of metabolite or metabolite plus API, then FDA should not set lower specifications than
157 the qualified level. In this case, we would recommend that the degradation product acceptance
158 criterion be set lower than the qualified level.

159
160 We recommend that ANDA sponsors develop robust formulations and manufacturing processes
161 that are based on sound state-of-the-art scientific and engineering principles and knowledge.
162 Although routine manufacturing variations are expected, significant variation in batch-to-batch
163 degradation product levels or an unusually high level of degradation products may indicate that
164 the manufacturing process of the drug product is not adequately controlled or designed. Although
165 the preceding statement is true, FDA must be sensitive for variables not linked to manufacturing
166 processes such as raw material variables. The previous statement enforces the notion that if
167 significant variation occurs, then it must be the process or the formula which is not robust.

168 **IV. QUALIFICATION OF DEGRADATION PRODUCTS**
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170 *Qualification* is the process of acquiring and evaluating data that establish the biological safety
171 of an individual degradation product or a given degradation profile at the level(s) being

172 considered. When appropriate, we recommend that applicants provide a rationale for establishing
173 degradation product acceptance criteria that includes safety considerations.

174
175 A degradation product is considered qualified when it meets one or more of the following
176 conditions:

- 177
178 • When the observed level and proposed acceptance criterion for the degradation product
179 do not exceed the level observed in an FDA-approved human drug product. In past
180 guidances, FDA acknowledged that due to the safety factors involved in the setting of
181 degradant specifications for RLD, a proposed product could have as much as twice the
182 level of degradants as those seen in the corresponding RLD. It is understood that now
183 OGD may want to tighten this criteria. However, the proposed wording leaves decisions
184 open to interpretation, which could lead to inconsistencies in review. It is proposed that
185 in order to accept higher levels of degradants, the qualitative formula of the proposed
186 product be the same as the RLD and that if this criteria is met, than an absolute
187 specification ceiling (i.e., NMT 25% RLD observed degradant levels) could be approved.
188 This is specially true in the case where degradants are clearly non-toxic (such as base
189 levels of a salt), or are active metabolites with same pharmacologic activity as the API.
- 190 • When the degradation product is a significant metabolite of the drug substance. Please
191 clarify what do you mean by “Significant”. Is a metabolite significant if there is evidence
192 that the pharmacologic activity of the metabolite is less than 90% that of the API?
- 193 • When the observed level and the proposed acceptance criterion for the degradation
194 product are adequately justified by the scientific literature.
- 195 • When the observed level and proposed acceptance criterion for the degradation product
196 do not exceed the level that has been adequately evaluated in toxicology studies.

197
198 Although Quantitative Structure Activity Relationships (QSAR) programs may be used for
199 prediction of toxicity of an individual degradation product or a given degradation profile, the
200 results are not generally considered conclusive for qualification purposes.

201 202 **A. Qualification Thresholds**

203
204 Recommended qualification thresholds³ for degradation products based on the maximum daily
205 dose of the drug are provided in ICH *Q3B(R)*. When these qualification thresholds are exceeded,
206 we recommend that degradation product levels be qualified. In some cases, it may be
207 appropriate to increase or decrease the qualification threshold for qualifying degradation
208 products. For example, when there is evidence that a degradation product in certain drug classes
209 or therapeutic classes has previously been associated with adverse reactions in patients, it may be
210 important to establish a lower qualification threshold. Conversely, when the concern for safety is
211 low, a higher threshold for qualifying degradation products may be appropriate. The FDA will
212 consider proposals for applications for alternative qualification thresholds on a case-by-case

³ *Qualification threshold* is defined as a limit above (>) which a degradation product should be qualified.

213 basis after considering issues such as patient population, drug class effects, and historical safety
214 data.

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216 **B. Qualification Procedures**

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218 The decision tree in Attachment 1 describes considerations for the qualification of degradation
219 products when the usual qualification threshold recommended in ICH *Q3B(R)* is exceeded. In
220 some cases, decreasing the level of the degradation product below the threshold rather than
221 providing additional data can be the simplest course of action. Alternatively, adequate data
222 could be available in the scientific literature to qualify the degradation product. The studies
223 considered appropriate to qualify the degradation product will depend on a number of factors,
224 including the patient population, daily dose, and route and duration of drug administration. Such
225 studies can be conducted on the drug product containing the degradation product to be controlled,
226 although studies using isolated degradation products can sometimes be appropriate. The
227 following are descriptions of methods for qualifying degradation products.

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229 *1. Comparative Analytical Studies*

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231 A degradation product present in a drug product covered by an ANDA can be qualified by
232 comparing the analytical profiles of a generic drug product with those in an approved human
233 drug product using the same validated, stability-indicating analytical procedure (e.g. comparative
234 HPLC studies). This approved human drug product is generally the reference listed drug (RLD).
235 However, you may also compare the profile to a different drug product with the same route of
236 administration and similar characteristics (e.g., tablet versus capsule) if samples of the reference
237 listed drug are unavailable or in the case of an ANDA submitted pursuant to a suitability petition.
238 It is essential that maximum daily doses of the degradation product and routes of administration
239 should be taken into account for qualification by comparative analytical studies. The qualified
240 threshold of a degradation product in a dosage form may not be applicable to all drug products
241 containing that degradation product if the maximum daily doses or the routes of administration
242 are different. We recommend that you conduct the stability studies on comparable samples (e.g.,
243 age of samples) to get a meaningful comparison of degradation profiles.

244

245 A degradation product present in the generic drug product is considered qualified if the amount
246 of identified degradation product in the generic drug product reflects the levels observed in the
247 corresponding approved human drug product.

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249 *2. Scientific Literature and Significant Metabolites*

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251 If the level of the specified identified degradation product is adequately justified by the scientific
252 literature, no further qualification is considered necessary. In addition, a degradation product
253 that is also a significant metabolite of the drug substance is generally considered qualified.

254

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256 literature, no further qualification is considered necessary. In addition, a degradation product
257 that is also a significant metabolite of the drug substance is generally considered qualified.

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3. *Toxicity Studies*

Toxicity tests are the least preferred method to qualify degradation products. We recommend the tests be used only when degradation products cannot be qualified by either of the above procedures (section IV.B.1 or 2). The tests are designed to detect compounds that induce general toxic or genotoxic effects in experimental systems. If performed, such studies should be conducted on the drug product or drug substance containing the degradation products to be controlled, although studies using isolated degradation products may also be used.