
Guidance for Industry Analytical Procedures and Methods Validation for Drugs and Biologics

DRAFT GUIDANCE

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

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CMC**

Guidance for Industry Analytical Procedures and Methods Validation for Drugs and Biologics

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1 **Guidance for Industry¹**
2 **Analytical Procedures and Methods Validation for Drugs and**
3 **Biologics**
4

5 This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current
6 thinking on this topic. It does not create or confer any rights for or on any person and does not operate to
7 bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of
8 the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA
9 staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call
10 the appropriate number listed on the title page of this guidance.
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15 **I. INTRODUCTION**
16

17 This revised draft guidance supersedes the 2000 draft guidance for industry on *Analytical*
18 *Procedures and Methods Validation*^{2,3} and, when finalized, will also replace the 1987 FDA
19 guidance for industry on *Submitting Samples and Analytical Data for Methods Validation*. It
20 provides recommendations on how you, the applicant, can submit analytical procedures⁴ and
21 methods validation data to support the documentation of the identity, strength, quality, purity,
22 and potency of drug substances and drug products.⁵ It will help you assemble information and
23 present data to support your analytical methodologies. The recommendations apply to drug
24 substances and drug products covered in new drug applications (NDAs), abbreviated new drug
25 applications (ANDAs), biologics license applications (BLAs), and supplements to these
26 applications. The principles in this revised draft guidance also apply to drug substances and drug
27 products covered in Type II drug master files (DMFs).
28

29 This revised draft guidance complements the International Conference on Harmonisation (ICH)
30 guidance *Q2(R1) Validation of Analytical Procedures: Text and Methodology (Q2(R1))* for
31 developing and validating analytical methods.
32

33 This revised draft guidance does not address investigational new drug application (IND) methods
34 validation, but sponsors preparing INDs should consider the recommendations in this guidance.
35 For INDs, sufficient information is required at each phase of an investigation to ensure proper
36 identity, quality, purity, strength, and/or potency. The amount of information on analytical
37 procedures and methods validation will vary with the phase of the investigation.⁶ For general

¹ This guidance has been prepared by the Office of Pharmaceutical Science, in the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

² Sample submission is described in section IX, FDA Methods Verification.

³ We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

⁴ *Analytical procedure* is interchangeable with a *method* or *test procedure*.

⁵ The terms *drug substance* and *drug product*, as used in this guidance, refer to human drugs and biologics.

⁶ See 21 CFR 312.23(a)(7).

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38 guidance on analytical procedures and methods validation information to be submitted for phase
39 one studies, sponsors should refer to the FDA guidance for industry on *Content and Format of*
40 *Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including*
41 *Well-Characterized, Therapeutic, Biotechnology-Derived Products*. General considerations for
42 analytical procedures and method validation (e.g., bioassay) before conduct of phase three
43 studies are discussed in the FDA guidance for industry on *IND Meetings for Human Drugs and*
44 *Biologics, Chemistry, Manufacturing, and Controls Information*.

45
46 This revised draft guidance does not address specific method validation recommendations for
47 biological and immunochemical assays for characterization and quality control of many drug
48 substances and drug products. For example, some bioassays are based on animal challenge
49 models, and immunogenicity assessments or other immunoassays have unique features that
50 should be considered during development and validation.

51
52 In addition, the need for revalidation of existing analytical methods may need to be considered
53 when the manufacturing process changes during the product's life cycle. For questions on
54 appropriate validation approaches for analytical procedures or submission of information not
55 addressed in this guidance, you should consult with the appropriate FDA product quality review
56 staff.

57
58 If you choose a different approach than those recommended in this revised draft guidance, we
59 encourage you to discuss the matter with the appropriate FDA product quality review staff before
60 you submit your application.

61
62 FDA's guidance documents, including this guidance, do not establish legally enforceable
63 responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should
64 be viewed only as recommendations, unless specific regulatory or statutory requirements are
65 cited. The use of the word *should* in Agency guidances means that something is suggested or
66 recommended, but not required.

67
68

69 **II. BACKGROUND**

70

71 Each NDA and ANDA must include the analytical procedures necessary to ensure the identity,
72 strength, quality, purity, and potency of the drug substance and drug product.⁷ Each BLA must
73 include a full description of the manufacturing methods, including analytical procedures that
74 demonstrate the manufactured product meets prescribed standards of identity, quality, safety,
75 purity, and potency.⁸ Data must be available to establish that the analytical procedures used in
76 testing meet proper standards of accuracy and reliability and are suitable for their intended
77 purpose.⁹ For BLAs and their supplements, the analytical procedures and their validation are
78 submitted as part of license applications or supplements and are evaluated by FDA quality
79 review groups.

80

⁷ See 21 CFR 314.50(d)(1) and 314.94(a)(9)(i).

⁸ See 21 CFR 601.2(a) and 601.2(c).

⁹ See 21 CFR 211.165(e) and 211.194(a)(2).

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81 Analytical procedures and validation data should be submitted in the corresponding sections of
82 the application in the ICH *M2 eCTD: Electronic Common Technical Document Specification*.¹⁰
83

84 When an analytical procedure is approved/licensed as part of the NDA, ANDA, or BLA, it
85 becomes the FDA approved analytical procedure for the approved product. This analytical
86 procedure may originate from FDA recognized sources (e.g., a compendial procedure from the
87 *United States Pharmacopeia/National Formulary* (USP/NF)) or a validated procedure you
88 submitted that was determined to be acceptable by FDA. To apply an analytical method to a
89 different product, appropriate validation studies with the matrix of the new product should be
90 considered.

91
92

93 **III. ANALYTICAL METHODS DEVELOPMENT**

94

95 An analytical procedure is developed to test a defined characteristic of the drug substance or
96 drug product against established acceptance criteria for that characteristic. Early in the
97 development of a new analytical procedure, the choice of analytical instrumentation and
98 methodology should be selected based on the intended purpose and scope of the analytical
99 method. Parameters that may be evaluated during method development are specificity, linearity,
100 limits of detection (LOD) and quantitation limits (LOQ), range, accuracy, and precision.

101

102 During early stages of method development, the robustness of methods should be evaluated
103 because this characteristic can help you decide which method you will submit for approval.
104 Analytical procedures in the early stages of development are initially developed based on a
105 combination of mechanistic understanding of the basic methodology and prior experience.
106 Experimental data from early procedures can be used to guide further development. You should
107 submit development data within the method validation section if they support the validation of
108 the method.

109

110 To fully understand the effect of changes in method parameters on an analytical procedure, you
111 should adopt a systematic approach for method robustness study (e.g., a design of experiments
112 with method parameters). You should begin with an initial risk assessment and follow with
113 multivariate experiments. Such approaches allow you to understand factorial parameter effects
114 on method performance. Evaluation of a method's performance may include analyses of
115 samples obtained from in-process manufacturing stages to the finished product. Knowledge
116 gained during these studies on the sources of method variation can help you assess the method
117 performance.

118

119

120 **IV. CONTENT OF ANALYTICAL PROCEDURES**

121

122 You should describe analytical procedures in sufficient detail to allow a competent analyst to
123 reproduce the necessary conditions and obtain results within the proposed acceptance criteria.
124 You should also describe aspects of the analytical procedures that require special attention. An
125 analytical procedure may be referenced from FDA recognized sources (e.g., USP/NF,

¹⁰ See sections 3.2.S.4 Control of Drug Substance, 3.2.P.4 Control of Excipients, and 3.2.P.5 Control of Drug Product.

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126 Association of Analytical Communities (AOAC) International)¹¹ if the referenced analytical
127 procedure is not modified beyond what is allowed in the published method. You should provide
128 in detail the procedures from other published sources. The following is a list of essential
129 information you should include for an analytical procedure:

130

131 **A. Principle/Scope**

132

133 A description of the basic principles of the analytical test/technology (separation, detection, etc.);
134 target analyte(s) and sample(s) type (e.g., drug substance, drug product, impurities or compounds
135 in biological fluids, etc.).

136

137 **B. Apparatus/Equipment**

138

139 All required qualified equipment and components (e.g., instrument type, detector, column type,
140 dimensions, and alternative column, filter type, etc.).

141

142 **C. Operating Parameters**

143

144 Qualified optimal settings and ranges (allowed adjustments) critical to the analysis (e.g., flow
145 rate, components temperatures, run time, detector settings, gradient, head space sampler). A
146 drawing with experimental configuration and integration parameters may be used, as applicable.

147

148 **D. Reagents/Standards**

149

150 The following should be listed:

151

- 152 • Grade of chemical (e.g., USP/NF, American Chemical Society, High
153 Performance or Pressure Liquid Chromatography, or Gas
154 Chromatography and preservative free).
- 155 • Source (e.g., USP reference standard or qualified in-house reference material).
- 156 • State (e.g., dried, undried, etc.) and concentration.
- 157 • Standard potencies (purity correction factors).
- 158 • Storage controls.
- 159 • Directions for safe use (as per current Safety Data Sheet).
- 160 • Validated or useable shelf life.

161

162 New batches of biological reagents, such as monoclonal antibodies, polyclonal antisera, or cells,
163 may need extensive qualification procedures included as part of the analytical procedure.

164

165 **E. Sample Preparation**

166

167 Procedures (e.g., extraction method, dilution or concentration, desalting procedures and mixing
168 by sonication, shaking or sonication time, etc.) for the preparations for individual sample tests.
169 A single preparation for qualitative and replicate preparations for quantitative tests with

¹¹ See 21 CFR 211.194(a)(2).

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170 appropriate units of concentrations for working solutions (e.g., $\mu\text{g/ml}$ or mg/ml) and information
171 on stability of solutions and storage conditions.

172

173 **F. Standards Control Solution Preparation**

174

175 Procedures for the preparation and use of all standard and control solutions with appropriate
176 units of concentration and information on stability of standards and storage conditions,
177 including calibration standards, internal standards, system suitability standards, etc.

178

179 **G. Procedure**

180

181 A step-by-step description of the method (e.g., equilibration times, and scan/injection sequence
182 with blanks, placebos, samples, controls, sensitivity solution (for impurity method) and
183 standards to maintain validity of the system suitability during the span of analysis) and allowable
184 operating ranges and adjustments if applicable.

185

186 **H. System Suitability**

187

188 Confirmatory test(s) procedures and parameters to ensure that the system (equipment,
189 electronics, and analytical operations and controls to be analyzed) will function correctly as an
190 integrated system at the time of use. The system suitability acceptance criteria applied to
191 standards and controls, such as peak tailing, precision and resolution acceptance criteria, may be
192 required as applicable. For system suitability of chromatographic systems, refer to CDER
193 reviewer guidance on *Validation of Chromatographic Methods* and USP General Chapter <621>
194 *Chromatography*.

195

196 **I. Calculations**

197

198 The integration method and representative calculation formulas for data analysis (standards,
199 controls, samples) for tests based on label claim and specification (e.g., assay, specified and
200 unspecified impurities and relative response factors). This includes a description of any
201 mathematical transformations or formulas used in data analysis, along with a scientific
202 justification for any correction factors used.

203

204 **J. Data Reporting**

205

206 A presentation of numeric data that is consistent with instrumental capabilities and acceptance
207 criteria. The method should indicate what format to use to report results (e.g., percentage label
208 claim, weight/weight, and weight/volume etc.) with the specific number of significant figures
209 needed. The American Society for Testing and Materials (ASTM) E29 describes a standard
210 practice for using significant digits in test data to determine conformance with specifications. For
211 chromatographic methods, you should include retention times (RTs) for identification with
212 reference standard comparison basis, relative retention times (RRTs) (known and unknown
213 impurities) acceptable ranges and sample results reporting criteria.

214

215

216 **V. REFERENCE STANDARDS AND MATERIALS**

217
218 Primary and secondary reference standards and materials are defined and discussed in the
219 following ICH guidances: *Q6A Specifications: Test Procedures and Acceptance Criteria for*
220 *New Drug Substances and New Drug Products: Chemical Substances (ICH Q6A)*, *Q6B*
221 *Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological*
222 *Products*, and *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical*
223 *Ingredients*. For all standards, you should ensure the suitability for use. Reference standards for
224 drug substances are particularly critical in validating specificity for an identity test. You should
225 strictly follow storage, usage conditions, and handling instructions for reference standards to
226 avoid added impurities and inaccurate analysis. For biological products, you should include
227 information supporting any reference standards and materials that you intend to use in the BLA
228 and in subsequent annual reports for subsequent reference standard qualifications. Information
229 supporting reference standards and materials include qualification test protocols, reports, and
230 certificates of analysis (including stability protocols and relevant known impurity profile
231 information, as applicable).

232
233 Reference standards can often be obtained from USP and may also be available through the
234 European Pharmacopoeia, Japanese Pharmacopoeia, World Health Organization, or National
235 Institute of Standards and Technology. Reference standards for a number of biological products
236 are also available from CBER. For certain biological products marketed in the U.S., reference
237 standards authorized by CBER must be used before the product can be released to the market.¹²
238 Reference materials from other sources should be characterized by procedures including routine
239 and beyond routine release testing as described in ICH Q6A. You should consider orthogonal
240 methods. Additional testing could include attributes to determine the suitability of the reference
241 material not necessarily captured by the drug substance or product release tests (e.g., more
242 extensive structural identity and orthogonal techniques for purity and impurities, biological
243 activity).

244
245 For biological reference standards and materials, we recommend that you follow a two-tiered
246 approach when qualifying new reference standards to help prevent drift in the quality attributes
247 and provide a long-term link to clinical trial material. A two-tiered approach involves a
248 comparison of each new working reference standard with a primary reference standard so that it
249 is linked to clinical trial material and the current manufacturing process.

250
251
252 **VI. ANALYTICAL METHOD VALIDATION FOR NDA, ANDAs, BLAs, AND**
253 **DMFs**

254
255 **A. Noncompendial Analytical Procedures**

256
257 Analytical method validation is the process of demonstrating that an analytical procedure is
258 suitable for its intended purpose. The methodology and objective of the analytical procedures
259 should be clearly defined and understood before initiating validation studies. This understanding

¹² See 21 CFR 610.20.

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260 is obtained from scientifically-based method development and optimization studies. Validation
261 data must be generated under an protocol approved by the sponsor following current good
262 manufacturing practices with the description of methodology of each characteristic test and
263 predetermined and justified acceptance criteria, using qualified instrumentation operated under
264 current good manufacturing practices conditions.¹³ Protocols for both drug substance and
265 product analytes or mixture of analytes in respective matrices should be developed and executed.

266
267 ICH Q2(R1) is considered the primary reference for recommendations and definitions on
268 validation characteristics for analytical procedures. The *FDA Reviewer Guidance: Validation of*
269 *Chromatographic Methods* is available as well.

270
271 **B. Validation Characteristics**

272
273 Although not all of the validation characteristics are applicable for all types of tests, typical
274 validation characteristics are:

- 275
276
- 277 • Specificity
 - 278 • Linearity
 - 279 • Accuracy
 - 280 • Precision (repeatability, intermediate precision, and reproducibility)
 - 281 • Range
 - 282 • Quantitation limit
 - 283 • Detection limit

284 If a procedure is a validated quantitative analytical procedure that can detect changes in a quality
285 attribute(s) of the drug substance and drug product during storage, it is considered a stability
286 indicating assay. To demonstrate specificity of a stability-indicating assay, a combination of
287 challenges should be performed. Some challenges include the use of samples spiked with target
288 analytes and all known interferences; samples that have undergone various laboratory stress
289 conditions; and actual product samples (produced by the final manufacturing process) that are
290 either aged or have been stored under accelerated temperature and humidity conditions.

291
292 As the holder of the NDA, ANDA, or BLA, you must:¹⁴ (1) submit the data used to establish
293 that the analytical procedures used in testing meet proper standards of accuracy and reliability,
294 and (2) notify the FDA about each change in each condition established in an approved
295 application beyond the variations already provided for in the application, including changes to
296 analytical procedures and other established controls.

297
298 The submitted data should include the results from the robustness evaluation of the method,
299 which is typically conducted during method development or as part of a planned validation
300 study.¹⁵

¹³ See 21 CFR 211.165(e); 21 CFR 314.50 (d), and for biologics see 21 CFR 601.2(a), 601.2(c), and 601.12(a).

¹⁴ For drugs see 21 CFR 314.50 (d), 314.70(d), and for biologics see 21 CFR 601.2(a), 601.2(c), and 601.12(a). For a BLA, as discussed below, you must obtain prior approval from FDA before implementing a change in analytical methods if those methods are specified in FDA regulations

¹⁵ See section III and ICH Q2(R1).

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C. Compendial Analytical Procedures

The suitability of an analytical procedure (e.g., USP/NF, the AOAC International Book of Methods, or other recognized standard references) should be verified under actual conditions of use.¹⁶ Compendial general chapters, which are complex and mention multiple steps and/or address multiple techniques, should be rationalized for the intended use and verified. Information to demonstrate that USP/NF analytical procedures are suitable for the drug product or drug substance should be included in the submission and generated under a verification protocol.

The verification protocol should include, but is not limited to: (1) compendial methodology to be verified with predetermined acceptance criteria, and (2) details of the methodology (e.g., suitability of reagent(s), equipment, component(s), chromatographic conditions, column, detector type(s), sensitivity of detector signal response, system suitability, sample preparation and stability). The procedure and extent of verification should dictate which validation characteristic tests should be included in the protocol (e.g., specificity, LOD, LOQ, precision, accuracy, etc.). Considerations that may influence what characteristic tests should be in the protocol may depend on situations such as whether specification limits are set tighter than compendial acceptance criteria, or RT or RRT profiles are changing in chromatographic methods because of the synthetic route of drug substance or differences in manufacturing process or matrix of drug product. Robustness studies of compendial assays do not need to be included, if methods are followed without deviations.

VII. STATISTICAL ANALYSIS AND MODELS

A. Statistics

Statistical analysis of validation data can be used to evaluate validation characteristics against predetermined acceptance criteria. All statistical procedures and parameters used in the analysis of the data should be based on sound principles and appropriate for the intended evaluation. Reportable statistics of linear regression analysis R (correlation coefficient), R square (coefficient of determination), slope, least square, analysis of variance (ANOVA), confidence intervals, etc., should be provided with justification. For information on statistical techniques used in making comparisons, as well as other general information on the interpretation and treatment of analytical data, appropriate literature or texts should be consulted.¹⁷

B. Models

Some analytical methods might use chemometric and/or multivariate models. When developing these models, you should include a statistically adequate number and range of samples for model development and comparable samples for model validation. Suitable software should be used for data analysis. Model parameters should be deliberately varied to test model robustness.

¹⁶ See 21 CFR 211.194(a)(2) and USP General Chapter <1226> *Verification of Compendial Procedures*.

¹⁷ See References section for examples including USP <1010> *Analytical Data – Interpretation and Treatment*.

345
346 **VIII. LIFE CYCLE MANAGEMENT OF ANALYTICAL PROCEDURES**
347

348 Once an analytical procedure (including compendial methods) is successfully validated and
349 implemented, the procedure will be followed during the life cycle of the product. Trend analysis
350 on method performance should be performed at regular intervals to evaluate the need to optimize
351 the analytical procedure or to revalidate all or a part of the analytical procedure. If an analytical
352 procedure can only meet the established system suitability requirements with repeated
353 adjustments to the operating conditions stated in the analytical procedure, the analytical
354 procedure should be reevaluated, revalidated, or amended, as appropriate.
355

356 Over the life cycle of a product, new information (e.g., a better understanding of product CQAs
357 or awareness of a new impurity) may warrant the development and validation of a new or
358 alternative analytical method. New technologies may allow for greater understanding and/or
359 confidence when ensuring product quality. Applicants should periodically evaluate the
360 appropriateness of a product's analytical methods and consider new or alternative methods.
361

362 In anticipation of life cycle changes in analytics, an appropriate number of samples should be
363 archived to allow for comparative studies. The number should be based on scientific principles
364 and an assessment of risk. For complex products that are sensitive to manufacturing changes,
365 archived samples can be an important tool to make these comparisons. The archived samples
366 used in comparative studies should include samples that represent pivotal clinical trial material
367 and marketed product.
368

369 If a risk-based evaluation or other drivers lead to changes in an analytical procedure or
370 replacement with a new method or if the procedure is transferred to a new testing site;
371 revalidation, a new validation exercise, an analytical method comparability study, or a
372 combination of these exercises should be considered. In some cases, changes to the drug
373 substance or drug product manufacturing process may also warrant analytical procedure
374 revalidation. These additional studies are discussed below.
375

376 **A. Revalidation**
377

378 Principles described in the validation section (section VI) apply to revalidation. When a change
379 is made to an analytical procedure (e.g., a change in a piece of equipment or reagent or because
380 of a change in manufacturing process or formulation), revalidation of all or part of the analytical
381 procedure should be considered. Analytical method revalidation may also be warranted because
382 of manufacturing process changes, such as an alteration in the drug substance manufacturing
383 process that could impact method performance (e.g., route of synthesis, fermentation) or
384 introduction of a new drug product formulation.
385

386 You should revalidate to ensure that the analytical procedure maintains its critical performance
387 characteristics (e.g., specificity, precision, accuracy, etc). The degree of revalidation depends on
388 the nature of the change.
389

B. Analytical Method Comparability Studies

Analytical method comparability study requests are typically generated when you propose to substitute an FDA approved analytical procedure with an alternative analytical procedure or when an analytical method is transferred from one laboratory to the other. These scenarios are discussed below.

1. Alternative Analytical Procedures

An alternative analytical procedure is an analytical procedure that you use in place of the FDA approved analytical procedure. For an NDA or ANDA, you should include any proposed alternate analytical procedures in the application. You must include a description of the procedure.¹⁸ After approval, for an NDA or ANDA, or for a procedure approved in a BLA but not included in an FDA regulation, the addition, revision, or deletion of an alternative analytical procedure that provides the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application, must be documented in the next annual report.¹⁹ Additions or revisions of analytical procedures in BLAs may require submission as a supplement. FDA recommends discussion with the appropriate review group to determine the appropriate reporting category

For biological products, rarely an analytical procedure may be included in an FDA regulation. When that occurs, alternative analytical procedures are submitted following 21 CFR 610.9(a). It states that the applicant will present evidence "...demonstrating that the modification will provide assurances of the safety, purity, potency, and effectiveness of the biological product equal to or greater than the assurances provided by the method or process specified in the general standards or additional standards for the biological product." Modification of such procedures requires FDA approval during application review or in a postapproval supplement.²⁰

You should identify the use of the alternative analytical procedure (e.g., release, stability testing) and provide a rationale for its inclusion, validation data, and comparative data to the FDA approved analytical procedure. You should perform a comparability study that demonstrates at a minimum that:

- The new method coupled with any additional control measures is equal or superior for the original method for the intended purpose.
- The new analytical procedure is not more susceptible to matrix effects than the original procedure.

If new process or product related variants or any new impurities are discovered with the new procedure, testing on archived samples from historical batches should be performed to demonstrate that the variants/impurities detected by the new method are a result of an increase in

¹⁸ See 21 CFR 314.50.

¹⁹ See 21 CFR 314.70(d)(1), (d)(2)(vii). 314.81(b)(2), and 601.12(d)(vii).

²⁰ See 21 CFR 610.9(b).

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432 the sensitivity or selectivity of the new procedure and not a result of a change to process related
433 impurities.

434

435 If the procedure has stability indicating properties:

436

- 437 • Appropriate samples should be included that allow a comparison of the ability of
438 the new and original method to detect relevant product variants and degradation
439 species.
- 440 • The number of batches analyzed for comparison should be statistically relevant
441 and justified for a pre-established confidence interval.
- 442 • Equivalence, non-inferiority, or superiority studies should be performed with
443 appropriate statistical methods to demonstrate that the new or revised method
444 performance is comparable or better than the original method.
- 445 • The statistical analyses performed to compare product testing should be
446 identified.
- 447 • All bias seen with comparative results should be discussed with an explanation, as
448 appropriate.

449

450 2. *Analytical Methods Transfer Studies*

451

452 Analytical method transfer is typically managed under an internal transfer protocol that details
453 the parameters to be evaluated in addition to the predetermined acceptance criteria that will be
454 applied to the results. Transfer studies usually involve two or more laboratories or sites
455 (originating lab and receiving labs) executing the preapproved transfer protocol. A sufficient
456 number of representative test articles (e.g., same lot(s) of drug substance or drug product) are
457 used by the originating and receiving laboratories. The comparative studies are performed to
458 evaluate accuracy and precision, especially with regard to assessment of interlaboratory
459 variability. In cases where the transferred analytical procedure is also a stability indicating
460 method, forced degradation samples or samples containing pertinent product-related impurities
461 should be analyzed at both sites. The USP General Chapter <1224> *Transfer of Analytical
462 Procedures* provides additional guidance on this topic.

463

464 **C. Reporting Postmarketing Changes to an Approved NDA, ANDA, or BLA**

465

466 Postmarketing changes to analytical procedures must be reported to the FDA in compliance with
467 21 CFR 314.70 or 21 CFR 601.12.²¹ Additional information on the appropriate reporting
468 category for various kinds of postapproval changes for NDAs and ANDAs is provided in the
469 FDA guidance for industry on *Changes to an Approved NDA or ANDA* and *Changes to an
470 Approved NDA or ANDA; Specifications – Use of Enforcement Discretion for Compendial
471 Changes*. Similar information on postapproval changes to BLAs regulated by CDER and CBER
472 is provided in the FDA guidance *Changes to an Approved Application for Specified
473 Biotechnology and Specified Synthetic Biological Products*.

474

475

²¹ As noted, for a product licensed under a BLA, if the change is to a procedure prescribed in FDA regulations that change must be approved by FDA pursuant to 21 CFR 610.9(b).

476 **IX. FDA METHODS VERIFICATION**

477
478 Part of the approval process for NDAs and ANDAs may include FDA laboratory assessment to
479 determine whether the analytical procedures are acceptable for quality control and suitable for
480 regulatory purposes.²² If a laboratory assessment will be conducted, the FDA laboratory will
481 send you a request that will detail what samples and supplies to send to the FDA laboratory.
482 These could include product samples, standards, critical reagents, material safety data sheets, and
483 supplies. Laboratory results and comments will be forwarded from the FDA laboratory to the
484 product quality reviewer.

485
486 For certain biological products, samples representative of the product for licensure along with
487 summaries of results of tests performed on the lots represented by these samples should be
488 submitted with the BLA.²³ The FDA laboratory verifies the performance of the methods and the
489 results you submit. During the pre-BLA meeting or after submission of the BLA, the FDA
490 laboratory can send you a request to provide standards, controls, reagents, material safety data
491 sheets, and supplies.

492
493
494 **X. REFERENCES**

495 **Guidance for Industry²⁴**

496
497
498 ANDAs: Impurities in Drug Products (November 2010)

499
500 ANDAs: Impurities in Drug Substances (July 2009)

501
502 Changes to an Approved NDA or ANDA (April 2004)

503
504 Changes to an Approved Application for Specified Biotechnology and Specified Synthetic
505 Biological Products (July 1997)

506
507 Changes to an Approved NDA or ANDA; Specifications – Use of Enforcement Discretion for
508 Compendial Changes (November 2004)

509
510 Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of
511 Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products (November
512 1995)

513
514 INDs for Phase 2 and 3 Studies of Drugs, Including Specified Therapeutic Biotechnology-
515 Derived Products (February 1999)

516

²² See 21 CFR 314.50(e).

²³ See 21 CFR 601.2(a).

²⁴ Draft guidances have been included for completeness only. As draft documents, they are not intended to be implemented until published in final form.

Contains Nonbinding Recommendations

Draft — Not for Implementation

517 Investigating Out of Specification (OOS) Test Results for Pharmaceutical Production (October
518 2006)

519
520 Submission of Chemistry, Manufacturing, and Controls Information for Synthetic Peptide
521 Substances (November 1994)

522
523 **Guidance for Industry: International Conference on Harmonization**

524
525 Q1A(R2) Stability Testing of New Drug Substances and Products (November 2003)

526
527 Q1B Stability Testing: Photostability Testing of New Drug Substances and Products (May
528 1997)

529
530 Q1C Stability Testing for New Dosage Forms (May 1997)

531
532 Q2(R1) Validation of Analytical Procedures: Text and Methodology (March 1995, May 1997)

533
534 Q3A(R2) Impurities in New Drug Substances (June 2008)

535
536 Q3B(R2) Impurities in New Drug Products (August 2006)

537
538 Q3C Impurities: Residual Solvents (December 1997)

539
540 Q3C Tables and List (February 2012)

541
542 Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological
543 Products (July 1996)

544
545 Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and
546 New Drug Products: Chemical Substances (December 2000)

547
548 Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological
549 Products (August 1999)

550
551 Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients
552 (August 2001)

553
554 **Reviewer Guidance**

555
556 Validation of Chromatographic Methods (November 1994)

557
558 **United States Pharmacopeia/National Formulary**

559
560 General Chapter <621> Chromatography

561
562 General Chapter <1010> Analytical Data – Interpretation and Treatment

Contains Nonbinding Recommendations

Draft — Not for Implementation

563
564 General Chapter <1224> Transfer of Analytical Procedures
565
566 General Chapter <1225> Validation of Compendial Procedures
567
568 General Chapter <1226> Verification of Compendial Procedures
569
570 General Notices and Requirements, Applying to Standards, Tests, Assays, and Other
571 Specifications of the United States Pharmacopeia: 7. Test Results
572
573 Interpretation and Treatment of Analytical Data; USP Pharmacopeial Forum, United States
574 Pharmacopeial Convention, Inc., Rockville MD: 1994, Volume 24, Number 5, pp. 7051 - 7056
575
576 **Other**
577
578 ASTM Standard, E29 - 2008 Standard Practice for Using Significant Digits in Test Data to
579 Determine Conformance with Specifications, ASTM International, West Conshohocken, PA,
580 (www.astm.org).
581
582 Miller, J.C., J.N. Miller, and E. Horwood, Statistics for Analytical Chemistry, 3rd edition,
583 Prentice
584 Hall, 1993.
585
586 Saunders, B.D., and R.G. Trapp, Basic and Clinical Biostatistics, 2nd edition, Appleton and
587 Lange,
588 1994.
589
590
591