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# Analytical Procedures and Methods Validation for Drugs and Biologics

## Guidance for Industry

**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)**

**July 2015  
Pharmaceutical Quality/CMC**

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

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# Analytical Procedures and Methods Validation for Drugs and Biologics Guidance for Industry<sup>1</sup>

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not create any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

## I. INTRODUCTION

This guidance supersedes the draft of the same name that published on February 19, 2014 (79 FR 9467) and replaces the 2000 draft guidance for industry on *Analytical Procedures and Methods Validation*<sup>2,3</sup> and the 1987 *Guidelines for Submitting Samples and Analytical Data for Methods Validation*. It provides recommendations on how you, the applicant, can submit analytical procedures<sup>4</sup> and methods validation<sup>5</sup> data to support the documentation of the identity, strength, quality, purity, and potency of drug substances and drug products.<sup>6</sup> It will help you assemble information and present data to support your analytical methodologies. The recommendations apply to drug substances and drug products covered in new drug applications (NDAs), abbreviated new drug applications (ANDAs), biologics license applications (BLAs), and supplements to these applications. The principles in this guidance also apply to drug substances and drug products covered in Type II drug master files (DMFs).

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

This guidance does not address investigational new drug application (IND) methods validation, but sponsors preparing INDs should consider the recommendations in this guidance. For INDs, sufficient information is required at each phase of an investigation to ensure proper identity, quality, purity, strength, and/or potency. The amount of information on analytical procedures and methods suitability will vary with the phase of the investigation.<sup>7</sup> For general guidance on

<sup>1</sup> This guidance has been prepared by the Office of Pharmaceutical Quality in the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

<sup>2</sup> Sample submission is described in section IX, FDA Methods Verification.

<sup>3</sup> 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>.

<sup>4</sup> *Analytical procedure* is interchangeable with a *method* or *test procedure*.

<sup>5</sup> Compendial methods are verified rather than validated as described in section VI, C.

<sup>6</sup> The terms *drug substance* and *drug product* are used in this guidance to refer to both human drugs and biologics.

<sup>7</sup> See 21 CFR 312.23(a)(7).

*Contains Nonbinding Recommendations*

37 analytical procedures and methods validation information to be submitted for phase one studies,  
38 sponsors should refer to the FDA guidance for industry on *Content and Format of*  
39 *Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including*  
40 *Well-Characterized, Therapeutic, Biotechnology-Derived Products*. General considerations for  
41 analytical procedures and methods validation before conduct of phase two and three studies are  
42 discussed in the FDA guidances for industry on *INDs for Phase 2 and 3 Studies of Drugs,*  
43 *Including Specified Therapeutic Biotechnology-Derived Products (February 1999)* and *IND*  
44 *Meetings for Human Drugs and Biologics, Chemistry, Manufacturing, and Controls*  
45 *Information*.

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

52  
53 Analytical methods required during product and process development activities are discussed in FDA  
54 guidance for industry on *Process Validation: General Principles and Practices*.

55  
56 In addition, a risk-based approach on the need for revalidation of existing analytical methods  
57 may need to be considered when the manufacturing process changes during the product's life  
58 cycle. For questions on appropriate validation approaches for analytical procedures or  
59 submission of information not addressed in this guidance, you should consult with the  
60 appropriate FDA quality assessment staff.

61  
62 If you choose a different approach than those recommended in this guidance, we encourage you  
63 to discuss the matter with the appropriate FDA quality assessment staff before you submit your  
64 application.

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

71  
72  
73 **II. BACKGROUND**

74  
75 Each NDA and ANDA must include the analytical procedures necessary to ensure the identity,  
76 strength, quality, purity, and potency of the drug substance and drug product.<sup>8</sup> Each BLA must  
77 include a full description of the manufacturing process, including analytical procedures that  
78 demonstrate the manufactured product meets prescribed standards of identity, quality, safety,  
79 purity, and potency.<sup>9</sup> Data must be available to establish that the analytical procedures used in

---

<sup>8</sup> See 21 CFR 314.50(d)(1) and 314.94(a)(9)(i).

<sup>9</sup> See 21 CFR 601.2(a) and 601.2(c).

80 testing meet proper standards of accuracy, sensitivity, specificity, and reproducibility and are  
81 suitable for their intended purpose.<sup>10</sup>

82  
83 Analytical procedures verification or validation data should be submitted in the corresponding  
84 sections of the application in the ICH *M2 eCTD: Electronic Common Technical Document*  
85 *Specification*.<sup>11</sup>

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

94  
95

### 96 **III. ANALYTICAL METHODS DEVELOPMENT**

97

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

104

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

112

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

121

122

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<sup>10</sup> See 21 CFR 211.165(e) and 211.194(a)(2).

<sup>11</sup> Sections as applicable in Module 3: 3.2.S and 3.2.P.

123 **IV. CONTENT OF ANALYTICAL PROCEDURES**

124  
125 You should describe analytical procedures in sufficient detail to allow a competent analyst to  
126 reproduce the necessary conditions and obtain results within the proposed acceptance criteria.  
127 You should also describe aspects of the analytical procedures that require special attention. An  
128 analytical procedure may be referenced from FDA-recognized sources (e.g., USP/NF,  
129 Association of Analytical Communities (AOAC) International)<sup>12</sup> if the referenced analytical  
130 procedure is not modified beyond what is allowed in the published method. You should provide  
131 in detail procedures from other published sources. The following is a list of essential  
132 information you should include for an analytical procedure:

133  
134 **A. Principle/Scope**

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

139  
140 **B. Apparatus/Equipment**

141  
142 All required qualified equipment and components (e.g., instrument type, detector, column type,  
143 dimensions, and alternative column, filter type).

144  
145 **C. Operating Parameters**

146  
147 Qualified optimal settings and ranges (include allowed adjustments supported by compendial  
148 sources or development and/or validation studies) critical to the analysis (e.g., flow rate,  
149 components temperatures, run time, detector settings, gradient, head space sampler). A drawing  
150 with experimental configuration and integration parameters may be used, as applicable.

151  
152 **D. Reagents/Standards**

153  
154 The following should be listed where applicable:

- 155  
156
- 157 • Description of reagent or standard
  - 158 • Grade of chemical (e.g., USP/NF, American Chemical Society, High  
159 Performance or Pressure Liquid Chromatography, or Gas  
Chromatography and preservative-free)
  - 160 • Source (e.g., USP reference standard, qualified in-house reference material,  
161 WHO International Standard/Reference Material, CBER standard)
  - 162 • Purity (for pure chemicals only), State (e.g., dried, undried), and concentration
  - 163 • Potencies (where required by CFR, USP)
  - 164 • Storage conditions
  - 165 • Directions for safe use (as per current Safety Data Sheet)
  - 166 • Validated or documented shelf life

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<sup>12</sup> See 21 CFR 211.194(a)(2).

167  
168 New batches of biological reagents, such as monoclonal antibodies, polyclonal antisera, or cells,  
169 may need extensive qualification procedures included as part of the analytical procedure.

170  
171 **E. Sample Preparation**

172  
173 Procedures (e.g., extraction method, dilution or concentration, desalting procedures and mixing  
174 by sonication, shaking or sonication time) for the preparations for individual sample tests. A  
175 single preparation for qualitative and replicate preparations for quantitative tests with appropriate  
176 units of concentrations for working solutions (e.g., µg/ml or mg/ml) and information on stability  
177 of solutions and storage conditions.

178  
179 **F. Standards Control Solution Preparation**

180  
181 Procedures for the preparation and use of all standard and control solutions with appropriate  
182 units of concentration and information on stability of standards and storage conditions,  
183 including calibration standards, internal standards, system suitability standards, etc.

184  
185 **G. Procedure**

186  
187 A step-by-step description of the method (e.g., equilibration times, and scan/injection sequence  
188 with blanks, placebos, samples, controls, sensitivity solution (for impurity method) and  
189 standards to maintain validity of the system suitability during the span of analysis) and allowable  
190 operating ranges and adjustments if applicable.

191  
192 **H. System Suitability**

193  
194 Confirmatory test(s) procedures and parameters to ensure that the system (equipment,  
195 electronics, and analytical operations and controls to be analyzed) will function correctly as an  
196 integrated system at the time of use. The system suitability acceptance criteria applied to  
197 standards controls and samples, such as peak tailing, precision and resolution acceptance criteria,  
198 may be required as applicable. For system suitability of chromatographic systems, refer to the  
199 FDA guidance for industry on *Validation of Chromatographic Methods* and USP General  
200 Chapter <621> *Chromatography*.

201  
202 **I. Calculations**

203  
204 The integration method and representative calculation formulas for data analysis (standards,  
205 controls, samples) for tests based on label claim and specification (e.g., assay, specified and  
206 unspecified impurities and relative response factors). This includes a description of any  
207 mathematical transformations or formulas used in data analysis, along with a scientific  
208 justification for any correction factors used.

209



210 **J. Data Reporting**

211  
212 A presentation of numeric data that is consistent with instrumental capabilities and acceptance  
213 criteria. The method should indicate what format to use to report results (e.g., percentage label  
214 claim, weight/weight, and weight/volume) with the specific number of significant figures  
215 needed. The American Society for Testing and Materials (ASTM) E29 standard describes a  
216 standard practice for using significant digits in test data to determine conformance with  
217 specifications. For chromatographic methods, you should include retention times (RTs) for  
218 identification with reference standard comparison basis, relative retention times (RRTs) (known  
219 and unknown impurities) acceptable ranges and sample results reporting criteria.  
220

221  
222 **V. REFERENCE STANDARDS AND MATERIALS**

223  
224 Primary and secondary reference standards and materials are defined and discussed in the  
225 following ICH guidances: *Q6B Specifications: Test Procedures and Acceptance Criteria for*  
226 *Biotechnological/Biological Products*, and *Q7 Good Manufacturing Practice Guidance for*  
227 *Active Pharmaceutical Ingredients*. For all standards, you should ensure the suitability for use.  
228 You should strictly follow storage and usage conditions and handling instructions for reference  
229 standards to avoid modifications and contaminations, which could result in additional impurities  
230 and inaccurate analysis. You should include information supporting any reference standards and  
231 materials that you intend to use in the application. Information supporting reference standards  
232 and materials should include qualification test reports and certificates of analysis (including  
233 stability protocols, reports, and relevant known impurity profile information) as applicable. For  
234 biological products under BLAs, qualification of subsequent reference standard lots should be  
235 included in annual reports.  
236

237 Reference standards can often be obtained from USP and may also be available through the  
238 European Pharmacopoeia, Japanese Pharmacopoeia, World Health Organization, or National  
239 Institute of Standards and Technology. Reference standards for a number of biological products  
240 are also available from CBER. For certain biological products marketed in the U.S., reference  
241 standards authorized by CBER must be used before the product can be released to the market.<sup>13</sup>  
242 Reference materials from other sources should be characterized by procedures including routine  
243 and beyond routine release testing as described in ICH Q6B. You should consider orthogonal  
244 methods for reference material characterization. Additional testing could include attributes to  
245 determine the suitability of the reference material not necessarily captured by the drug substance  
246 or product release tests (e.g., more extensive structural identity and orthogonal techniques for  
247 potency, purity and impurities).  
248

249 A new batch of reference standard material (official or in-house) should be qualified/calibrated  
250 against the current reference standard. For biological reference standards and materials, we  
251 recommend that you follow a two-tiered approach when qualifying new reference standards to  
252 prevent drift in the quality attributes. A two-tiered approach involves a comparison of each new

---

<sup>13</sup> See 21 CFR 610.20.

253 reference standard with a primary reference standard so that it is linked to clinical trial material  
254 and the current manufacturing process.

255  
256

## 257 **VI. ANALYTICAL METHOD VALIDATION**

258  
259

### **A. Noncompendial Analytical Procedures**

260

261 Analytical method validation is the process of demonstrating that an analytical procedure is  
262 suitable for its intended purpose. The methodology and objective of the analytical procedures  
263 should be clearly defined and understood before initiating validation studies. This understanding  
264 is obtained from scientifically-based method development and optimization studies. Validation  
265 data must be generated under a protocol approved by the sponsor following current good  
266 manufacturing practices with the description of methodology of each validation characteristic  
267 and predetermined and justified acceptance criteria, using qualified instrumentation.<sup>14</sup> Protocols  
268 for both drug substance and product analytes or mixture of analytes in respective matrices should  
269 be developed and executed. You should include details of the validation studies and results with  
270 your application.

271

### **B. Validation Characteristics**

272

273

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

276

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

284

285 ICH Q2(R1) is considered the primary reference for recommendations and definitions on  
286 validation characteristics for analytical procedures. The FDA guidance for industry on  
287 *Validation of Chromatographic Methods* is available as well.

288

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

296

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<sup>14</sup> For drugs 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).

297 As the holder of the NDA, ANDA, or BLA, you must: (1) submit the data used to establish that  
298 the analytical procedures used in testing meet proper standards of accuracy and reliability, and  
299 (2) notify the FDA about each change in each condition established in an approved application  
300 beyond the variations already provided for in the application, including changes to analytical  
301 procedures and other established controls.<sup>15</sup>

302  
303 The submitted data should include the results from the robustness evaluation of the method,  
304 which is typically conducted during method development or as part of a planned validation  
305 study.<sup>16</sup>

### 306 **C. Compendial Analytical Procedures**

307  
308 The suitability of an analytical procedure (e.g., USP/NF, the Official Methods of Analysis of  
309 AOAC International, or other recognized standard references) should be verified under actual  
310 conditions of use.<sup>17</sup> Information to demonstrate that USP/NF analytical procedures are suitable  
311 for the drug product or drug substance should be included in the submission and generated under  
312 a verification protocol.

313  
314 The verification protocol should include, but is not limited to: (1) compendial methodology to  
315 be verified with predetermined acceptance criteria, and (2) details of the methodology (e.g.,  
316 suitability of reagent(s), equipment, component(s), chromatographic conditions, column, detector  
317 type(s), sensitivity of detector signal response, system suitability, sample preparation and  
318 stability). The procedure and extent of verification should dictate which validation characteristic  
319 tests should be included in the protocol (e.g., specificity, LOD, LOQ, precision, accuracy).  
320 Considerations that may influence what characteristic tests should be in the protocol may depend  
321 on situations such as whether specification limits are set tighter than compendial acceptance  
322 criteria, or RT or RRT profiles are changing in chromatographic methods because of the  
323 synthetic route of drug substance or differences in manufacturing process or matrix of drug  
324 product. Robustness studies of compendial assays do not need to be included, if methods are  
325 followed without deviations.

## 326 327 328 **VII. STATISTICAL ANALYSIS AND MODELS**

### 329 **A. Statistics**

330  
331 Statistical analysis of validation data can be used to evaluate validation characteristics against  
332 predetermined acceptance criteria. All statistical procedures and parameters used in the analysis  
333 of the data should be based on sound principles and appropriate for the intended evaluation.  
334 Several statistical methods are useful for assessing validation characteristics, for example, an  
335 analysis of variance (ANOVA) to assess regression analysis R (correlation coefficient) and R

---

<sup>15</sup> 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, you must obtain prior approval from FDA before implementing a change in analytical methods if those methods are specified in FDA regulations.

<sup>16</sup> See section III and ICH Q2(R1).

<sup>17</sup> See 21 CFR 211.194(a)(2) and USP General Chapter <1226> *Verification of Compendial Procedures*.

squared (coefficient of determination) or linear regression to measure linearity. Many statistical methods used for assessing validation characteristics rely on population normality, and it is important to determine whether or not to reject this assumption. There are many techniques, such as histograms, normality tests, and probability plots that can be used to evaluate the observed distribution. It may be appropriate to transform the data to better fit the normal distribution or apply distribution-free (nonparametric) approaches when the observed data are not normally distributed. Appropriate literature or text should be consulted for information on statistical procedures to use when developing new test methods, evaluating existing test methods or evaluating measurement system performance, as well as other general information on the interpretation and treatment of analytical data.<sup>18</sup> The data analysis should be assured either by using appropriately validated software or independent verification for correctness.

## **B. Models**

Some analytical methods might use chemometric and/or multivariate models. When developing these models, the number of samples to provide adequate statistical power and range for model development and validation should be considered. Suitable software should be used for data analysis. Model parameters should be deliberately varied to test model robustness.

## **VIII. LIFE CYCLE MANAGEMENT OF ANALYTICAL PROCEDURES**

Once an analytical procedure (including compendial methods) is successfully validated (or verified) and implemented, the procedure should be followed during the life cycle of the product to continually assure that it remains fit for its intended purpose. Trend analysis on method performance should be performed at regular intervals to evaluate the need to optimize the analytical procedure or to revalidate all or a part of the analytical procedure. If an analytical procedure can only meet the established system suitability requirements with repeated adjustments to the operating conditions stated in the analytical procedure, the analytical procedure should be reevaluated, revalidated, or amended, as appropriate.

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

In anticipation of life cycle changes in analytics, an appropriate number of retention samples should be maintained to allow for comparative studies. The number should be based on scientific principles and an assessment of risk. For complex products that are sensitive to manufacturing changes, reserve samples can be an important tool to make these comparisons.

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<sup>18</sup> See References section for examples including USP <1010> *Analytical Data – Interpretation and Treatment*, ASTM E1488 *Standard Guide for Statistical Procedures to Use in Developing and Applying Test Methods* and ASTM E2782 *Standard Guide for Measurement Systems Analysis*.

380 The retention samples used in comparative studies should include samples that represent  
381 marketed product and, when possible, pivotal clinical trial material.

382  
383 If a risk-based evaluation or other drivers lead to changes in an analytical procedure or  
384 replacement with a new method or if the procedure is transferred to a new testing site;  
385 revalidation, a new validation exercise, an analytical method comparability study, or a  
386 combination of these exercises should be considered. In some cases, changes to the drug  
387 substance or drug product manufacturing process may also warrant analytical procedure  
388 revalidation. These additional studies are discussed below.

389  
390 **A. Revalidation**

391  
392 Principles described in the validation section (section VI) apply to revalidation. When a change  
393 is made to an analytical procedure (e.g., a change in a piece of equipment or reagent or because  
394 of a change in manufacturing process or formulation), revalidation of all or part of the analytical  
395 procedure should be considered. Analytical method revalidation may also be warranted because  
396 of manufacturing process changes, such as an alteration in the drug substance manufacturing  
397 process that could impact method performance (e.g., route of synthesis, fermentation) or  
398 introduction of a new drug product formulation.

399  
400 You should revalidate to ensure that the analytical procedure maintains its critical performance  
401 characteristics (e.g., specificity, precision, accuracy). The degree of revalidation depends on the  
402 nature of the change.

403  
404 **B. Analytical Method Comparability Studies**

405  
406 Analytical method comparability study requests are typically generated when you propose to  
407 substitute an FDA-approved analytical procedure with an alternative analytical procedure or  
408 when an analytical method is transferred from one laboratory to the other. For information on  
409 statistical procedures to use for determining equivalence of two test methods, appropriate  
410 literature or text should be consulted.<sup>19</sup> These scenarios are discussed below.

411  
412 *1. Alternative Analytical Procedures*

413  
414 An alternative analytical procedure is an analytical procedure that you use in place of the FDA-  
415 approved analytical procedure. For an NDA or ANDA, you should include any proposed  
416 alternate analytical procedures in the application. You must include a description of the  
417 procedure.<sup>20</sup> After approval, for an NDA or ANDA, or for a procedure approved in a BLA but  
418 not included in an FDA regulation, the addition, revision, or deletion of an alternative analytical  
419 procedure that provides the same or increased assurance of the identity, strength, quality, purity,

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<sup>19</sup> See References section for examples including USP General Chapter <1010> *Analytical Data – Interpretation and Treatment* and ASTM E2935 *Standard Practice for Conducting Equivalence Testing in Laboratory Applications*.

<sup>20</sup> See 21 CFR 314.50.

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420 or potency of the material being tested as the analytical procedure described in the approved  
421 application, must be documented in the next annual report.<sup>21</sup>

422  
423 For biological products, in rare cases an analytical procedure may be included in an FDA  
424 regulation. If the analytical method required is described by a regulation, however, and you want  
425 to use an alternate method, you must submit the alternate method for review and approval  
426 according to 21 CFR 610.9(a). You must present evidence "...demonstrating that the  
427 modification will provide assurances of the safety, purity, potency, and effectiveness of the  
428 biological product equal to or greater than the assurances provided by the method or process  
429 specified in the general standards or additional standards for the biological product."

430 Modification of such procedures requires FDA approval during application review or in a  
431 postapproval supplement.<sup>22</sup>

432  
433 You should identify the use of the alternative analytical procedure (e.g., release, stability testing)  
434 and provide a rationale for its inclusion, validation data, and comparative data to the FDA-  
435 approved analytical procedure. You should perform an analytical method comparability study  
436 that demonstrates at a minimum that:

- 437
- 438 • The new method coupled with any additional control measures is equivalent or  
439 superior to the original method for the intended purpose.
  - 440
  - 441 • The new analytical procedure is not more susceptible to matrix effects than the  
442 original procedure.
  - 443

444 If new process-related or product-related variants or any new impurities are discovered with the  
445 new procedure, testing on retention samples from historical batches should be performed to  
446 demonstrate that the variants/impurities detected by the new method are a result of an increase in  
447 the sensitivity or selectivity of the new procedure and not a result of a change to process-related  
448 impurities.

449  
450 If the procedure has stability-indicating properties:

- 451
- 452 • Appropriate samples should be included that allow a comparison of the ability of  
453 the new and original method to detect relevant product variants and degradation  
454 species.
  - 455 • The number of batches analyzed for comparison should provide sufficient  
456 statistical power.
  - 457 • Equivalence, non-inferiority, or superiority studies should be performed with  
458 appropriate statistical methods to demonstrate that the new or revised methods  
459 performance is comparable or better than the original method.<sup>23</sup>
  - 460 • The statistical analyses performed to compare product testing should be  
461 identified.

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<sup>21</sup> See 21 CFR 314.70(d)(1), (d)(2)(vii). 314.81(b)(2), and 601.12(d)(vii).

<sup>22</sup> See 21 CFR 610.9(b).

<sup>23</sup> ASTM E2935 – Standard Practice for Conducting Equivalence Testing in Laboratory Applications.

- All bias or differences between analytical procedures seen with comparative results should be discussed with an explanation, as appropriate.

## 2. *Analytical Methods Transfer Studies*

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

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

Postmarketing changes to analytical procedures must be reported to the FDA in compliance with 21 CFR 314.70 or 21 CFR 601.12.<sup>24</sup> Additional information on the appropriate reporting category for various kinds of postapproval changes for NDAs and ANDAs is provided in the FDA guidance for industry on *Changes to an Approved NDA or ANDA* and *Changes to an Approved NDA or ANDA; Specifications – Use of Enforcement Discretion for Compendial Changes*. Similar information on postapproval changes to BLAs regulated by CDER and CBER is provided in the FDA guidance *Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products*.

## **IX. FDA METHODS VERIFICATION**

Part of the approval process for NDAs and ANDAs may include FDA laboratory assessment to determine whether the analytical procedures are acceptable for quality control and suitable for regulatory purposes.<sup>25</sup> If a laboratory assessment will be conducted, the FDA laboratory will send you a request that will detail what samples and supplies to send to the FDA laboratory. These could include product samples, standards, critical reagents, material safety data sheets, and supplies. Laboratory results and comments will be forwarded from the FDA laboratory to the product quality reviewer.

For certain biological products, samples representative of the product for licensure along with summaries of results of tests performed on the lots represented by these samples should be submitted with the BLA.<sup>26</sup> The FDA laboratory verifies the performance of the methods and the

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<sup>24</sup> 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).

<sup>25</sup> See 21 CFR 314.50(e).

<sup>26</sup> See 21 CFR 601.2(a).

504 results you submit. During a pre-BLA meeting or after submission of the BLA, the FDA  
505 laboratory can send you a request to provide standards, controls, reagents, material safety data  
506 sheets, and supplies.

507

## 508 **X. REFERENCES**

509

### 510 **Guidance for Industry<sup>27</sup>**

511

512 ANDAs: Impurities in Drug Products (November 2010)

513

514 ANDAs: Impurities in Drug Substances (July 2009)

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516 Changes to an Approved NDA or ANDA (April 2004)

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518 Changes to an Approved Application for Specified Biotechnology and Specified Synthetic  
519 Biological Products (July 1997)

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

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524 Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of  
525 Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products (November  
526 1995)

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528 IND Meetings for Human Drugs and Biologics, Chemistry Manufacturing and Controls  
529 Information (May 2001)

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

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534 Investigating Out of Specification (OOS) Test Results for Pharmaceutical Production (October  
535 2006)

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537 Process Validation: General Principles and Practices (January 2011)

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539 Reviewer Guidance, Validation of Chromatographic Methods (November 1994)

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541 Submission of Chemistry, Manufacturing, and Controls Information for Synthetic Peptide  
542 Substances (November 1994)

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<sup>27</sup> Draft guidances have been included for completeness only. As draft documents, they are not intended to be implemented until published in final form. 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>.



544	<b>Guidance for Industry: International Conference on Harmonization</b>
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546	Q1A(R2) Stability Testing of New Drug Substances and Products (November 2003)
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548	Q1B Stability Testing: Photostability Testing of New Drug Substances and Products (May
549	1997)
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551	Q1C Stability Testing for New Dosage Forms (May 1997)
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553	Q2(R1) Validation of Analytical Procedures: Text and Methodology (March 1995, May 1997)
554	
555	Q3A(R2) Impurities in New Drug Substances (June 2008)
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557	Q3B(R2) Impurities in New Drug Products (August 2006)
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559	Q3C Impurities: Residual Solvents (December 1997)
560	
561	Q3C Tables and List (February 2012)
562	
563	Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological
564	Products (July 1996)
565	
566	Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and
567	New Drug Products: Chemical Substances (December 2000)
568	
569	Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological
570	Products (August 1999)
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572	Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients
573	(August 2001)
574	
575	<b>United States Pharmacopeia/National Formulary</b>
576	
577	General Chapter <621> Chromatography
578	
579	General Chapter <1010> Analytical Data – Interpretation and Treatment
580	
581	General Chapter <1224> Transfer of Analytical Procedures
582	
583	General Chapter <1225> Validation of Compendial Procedures
584	
585	General Chapter <1226> Verification of Compendial Procedures
586	
587	General Notices and Requirements, Applying to Standards, Tests, Assays, and Other
588	Specifications of the United States Pharmacopeia: 7. Test Results
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591 Pharmacopeial Convention, Inc., Rockville MD: 1994, Volume 24, Number 5, pp. 7051 - 7056

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593 **Other**

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602 ASTM E2782 – Standard Guide for Measurement Systems Analysis (MSA), ASTM  
603 International, West Conshohocken, PA, ([www.astm.org](http://www.astm.org)).

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605 ASTM Standard, E2935 – 2013 Standard Practice for Conducting Equivalence Testing in  
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