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Ref.: *DRAFT Guidance for Industry ChromPAC, Manufacturing Chromatography Systems Post-approval Changes: Chemistry, Manufacturing and Controls Document* submitted to Docket #03N-0059 - *Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach*

Dear Sir/Madam:

PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical and biopharmaceutical manufacturing and quality.

PDA is pleased to provide this original proposal for a DRAFT Industry Guidance entitled *DRAFT Guidance for Industry ChromPAC, Manufacturing Chromatography Systems Post-approval Changes: Chemistry, Manufacturing and Controls Document* to Docket number 03N-0059 as a proposed guidance for post-approval change for FDA's future consideration under the *Pharmaceutical cGMPs for the 21st Century: A Risk Basked Approach Initiative*. FDA's recent risk management initiatives have addressed incorporating best practices to simplify the regulatory requirements and reduce regulatory reporting burden through a risk-based approach contingent on the level of scientific understanding of how manufacturing process factors affect product performance. The proposed industry guidance is consistent with FDA's stated goal of identifying opportunities for reducing application submission and filing requirements. It offers a framework for FDA and industry to agree on the appropriate reporting level and test documentation requirements based on the potential for a given change to adversely affect the product. The proposed guidance addresses post-approval changes to drug substance manufacturing processes for chromatography systems.

The proposed guidance describes chemistry, manufacturing, and controls information and documentation in support of each change and provides recommendations on reporting categories based on the potential for a specified change to have an adverse effect on the drug substance/drug product. It would permit less burdensome notice of certain chromatography systems post-approval changes contingent on the applicant providing the

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appropriate test documentation as outlined in this proposed guidance for industry.

The proposed guidance includes change tables that define: 1) levels of change; 2) examples of changes within that level; 3) recommended chemistry, manufacturing, and controls test documentation for each level of change; and 4) filing category for the chromatography system change(s). The proposed guidance accordingly sets forth application information that should be provided to assure continuing product quality and performance characteristics of products for specified post-approval changes. The proposed guidance emphasizes the need to compare the product derived from the modified process to the one derived from the currently registered process, essentially to ascertain that introduction of the change(s) did not alter the physico-chemical and biological characteristics of the product.

If you have any questions regarding our proposal, or how we may assist with further development of the Guidance, please contact me.

Yours sincerely,

A handwritten signature in cursive script that reads "Victoria Ann Detrick". The signature is written in black ink and is positioned above the typed name.

Victoria Ann Detrick
Vice President, Quality and Regulatory Affairs
PDA

DRAFT

Guidance for Industry

ChromPAC

**Manufacturing Chromatography Systems
Postapproval Changes: Chemistry,
Manufacturing and Controls Documentation**

TABLE OF CONTENTS

	Page
15	
16	
17	
18	
19	I. INTRODUCTION 3
20	
21	II. PURPOSE OF GUIDANCE..... 4
22	
23	III. GENERAL CONSIDERATIONS 5
24	
25	IV. ASSESSMENT OF CHANGE 6
26	Comparability of Impurity Profiles 7
27	Product and Process Related Substances 8
28	Comparability of Physical Properties 11
29	
30	V. TYPES OF CHANGES 12
31	Documentation..... 12
32	Change Tables 13
33	
34	1. MOBILE PHASE 14
35	
36	2. STATIONARY PHASE 16
37	
38	3. CHROMATOGRAPHIC CONDITIONS 18
39	
40	4. EQUIPMENT 22
41	
42	5. CHANGES IN COLUMN SIZE (Scale Up/Scale Down)..... 25
43	
44	6. ADDITION/SUBTRACTION OF DUPLICATE COLUMN(S)..... 28
45	
46	7. SITE CHANGES 31
47	
48	8. MULTIPLE RELATED CHANGES 35
49	
50	VI. REFERENCES 36
51	
52	APPENDIX A: FACTORS TO CONSIDER 37
53	
54	APPENDIX B: CHARACTERIZATION 38
55	
56	APPENDIX C: GLOSSARY 39

I. INTRODUCTION

On November 21, 1997, the President signed the Food and Drug Administration Modernization Act (the Modernization Act). Section 116 of the Modernization Act amended the Food, Drug, and Cosmetic Act (the Act) by adding section 506A (21 U.S.C. 356a), which provides requirements for making and reporting manufacturing changes to an approved application and for distributing a drug product made with such changes.

Under section 506A of the Act, and Section 351 of the Public Health Service Act (PHS Act), the holder of a new drug application (NDA), abbreviated new drug application (ANDA), abbreviated antibiotic application (AADA), or Biologic License Applications (BLA) must notify FDA about each change in each condition established in an approved application beyond the variations already provided for in the application. The Act provides for four reporting categories: (1) Prior Approval Supplement (PAS), (2) Supplement – Changes Being Effectuated in 30 days (CBE-30), (3) Supplement – Changes Being Effectuated (CBE-0), and (4) Annual Report (AR). The reporting category for a change is based on the potential for the change to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or efficacy of the drug product. The changes that require prior approval are those that have a substantial potential to have an adverse effect, CBE-30 and CBE have a moderate potential to have an adverse effect, and those reported in an AR have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or efficacy of the drug product.

Regulations described in the Code of Federal Regulations (CFR) (specifically, 21CFR314.70(g) and 601.12), section 506A of the FD&C Act, various guidance documents previously issued by FDA interpreting the regulations, and the Act currently, prescribe the requirements for reporting changes for approved drugs and licensed biological products to FDA, and provide guidance on the proper reporting category. Before distributing a product made using a change, applicants are required to demonstrate, through appropriate validation and/or other clinical or non-clinical laboratory studies, the lack of adverse effect of the change on the identity, strength, quality, purity, or potency as they may relate to the safety or effectiveness of the product.

Under the regulations and guidance, an applicant can submit one or more protocols (i.e., comparability protocols) describing tests, validation studies, and acceptable limits to be achieved to demonstrate the absence of an adverse effect from specified types of changes. A comparability protocol can be used to reduce the reporting category (usually by one level) for specified changes. A proposed comparability protocol is submitted as a prior approval supplement, if not approved as part of the original application. FDA has recently issued guidance documents on comparability protocols for both small and large molecules. It is expected that the changes discussed in this document are of the type that may be suitable for submission in a comparability protocol.

101 **II. PURPOSE AND SCOPE OF GUIDANCE**

102
103 This document is issued to provide manufacturers with guidance on post approval changes
104 for chromatographic manufacturing systems. Improvement of product quality, process
105 economics, increase in production yield and/or global harmonization of operating
106 parameters are the main reasons for introduction of chromatography system changes. The
107 intention of the document is to provide manufacturers with increased flexibility and clarity
108 when reporting changes to chromatographic operations in an approved manufacturing
109 process, while ensuring patient safety, drug efficacy and quality. This document provides
110 guidance for post-approval changes to manufacturing process chromatography systems in
111 the production of drug substance that is used for both chemically synthesized drug products
112 and human specified biological products as outlined in 21 CFR 601.2 (with the exception of
113 therapeutic DNA plasmid products) regulated by the Center for Drugs Evaluation and
114 Research (CDER) or the Center for Biologics Evaluation and Research (CBER).

115
116 This guidance provides recommendations to sponsors of NDAs, ANDAs, AADAs, drug
117 master files (DMFs) and BLAs who intend, during the post-approval period, to change: 1)
118 the components or composition of the mobile phase; 2) the composition (solid support
119 and/or moiety) of the stationary phase; 3) chromatographic loads and other operating
120 conditions; 4) the composition of column equipment; 5) the scale-up/scale-down of the
121 column(s); 6) addition or subtraction of columns (number of duplicate columns or process
122 steps); and/or 7) the site of manufacture where a chromatography system is used.

123
124 This guidance provides recommendations on reporting categories under the post approval
125 change regulations, and guidance as they relate to chromatography systems in drug
126 substance manufacturing processes and provides recommendations on the chemistry,
127 manufacturing and controls information that should be provided to CDER or CBER to
128 ensure continued drug substance and drug product quality and performance characteristics.
129 This guidance further emphasizes the necessity to compare the product derived from the
130 modified process to the one derived from the currently approved process. This evaluation
131 is meant to confirm that introduction of the change(s) did not alter the physico-chemical
132 and/or biological characteristics of the product, and therefore the identity, strength, quality,
133 purity, or potency of the drug product as these factors may relate to the safety and efficacy
134 of the drug product.

135
136 Post-approval changes to chromatography systems used in the analytical testing procedures
137 or the manufacture of raw material/starting materials/excipients/reagents used in drug
138 substance/drug product process are not addressed in this document.

139
140 This guidance provides for a lower reporting level for certain chromatography systems
141 post-approval changes contingent on the applicant providing the appropriate information as
142 outlined in this guidance. This guidance does not affect any post-approval changes other
143 than the ones specified.

145 This guidance does not comment on or otherwise affect compliance or inspection
146 documentation that has been defined by the office of Compliance or FDA's Office of
147 Regulatory Affairs. Applicants can contact the appropriate chemistry review teams for
148 guidance on post-approval changes not addressed in these information sources.

149

150 **III. GENERAL CONSIDERATIONS**

151

152 Note: Comparability is the term most commonly used for biologic molecules while
153 equivalence is the term most commonly used for small molecules. In this guidance, the
154 term comparability is used to describe and encompass both terms.

155

156 It is the responsibility of the manufacturer to assess to what extent the proposed
157 chromatography change(s) has the potential to have an adverse effect on the product. A
158 sponsor may be able to demonstrate product comparability between material made after a
159 manufacturing change and material made before implementation of the change through
160 different types of analytical and functional testing (including bioassays for complex
161 biological molecules such as mAbs) described in this document. The manufacturer should
162 fully assess the intent of the chromatography step and the strength of the analytical tests in
163 the assessment of the impact the change will have on the product. For example, a change in
164 a chromatography cleaning wash step may, in one instance, have little safety impact, but
165 could be crucial if the wash step is important in the removal of adventitious agents (and in
166 the ability to measure that removal).

167

168 In determining the types of tests needed, the extent of the manufacturing change(s) and the
169 stage of manufacturing at which the change(s) occurs (e.g. early recovery vs. late
170 purification) must be considered. In particular, reporting categories for a given process
171 change may depend on whether the change occurs pre- or post-final intermediate for a
172 synthetic chemical compound.

173

174 It is recognized that no guidance document can address every circumstance, and that this
175 document will have limitations in addressing each manufacturer's particular case. In
176 addition, predictions of patient safety and drug efficacy are influenced by many factors
177 besides the manufacturing step, for example: (1) ability to fully analyze and characterize a
178 molecule varies depending on its complexity (e.g., acetaminophen versus insulin, versus a
179 monoclonal antibody); (2) understanding of the mechanism of action varies from product to
180 product and disease to disease (e.g., diabetes versus rheumatoid arthritis); (3) complexity of
181 a clinical indication (diabetes versus post-chemotherapy supportive therapy); (4)
182 understanding of the basis of toxicity (e.g., acetaminophen overdose versus
183 immunogenicity) and (5) physical properties in relationship to dosage form. Considering
184 the complexity and interdependence of these factors, it is acknowledged that there are limits
185 to providing a universal and prescriptive set of rules.

186

187 Manufacturers should provide to the FDA adequate chemical and physical (and in some
188 cases biological) comparisons with side-by-side analyses of the "old" and "new" materials
189 and demonstrating that the postchange material is comparable to the prechange material.

190 For small molecules, the impact of the manufacturing change can be evaluated in isolated
191 intermediates following the process step in which the manufacturing modification is made.
192 For biotechnology-derived products, comparison to a reference standard may be appropriate
193 and applicants should consider the need to perform pharmacokinetic/pharmacodynamic
194 (PK/PD) studies even in cases where the chemical/physical testing shows comparability.

195
196 Tests should include those routinely used for release of the active pharmaceutical
197 ingredient, and where appropriate additional tests specifically directed at fully evaluating
198 the impact of the change. A re-evaluation of the in-process controls should be undertaken
199 to ensure that appropriate monitoring is performed at the critical decision making steps and
200 at points where data serve to confirm consistency of the process. A re-assessment of the
201 critical controls - those that must be controlled with predetermined criteria to ensure that the
202 drug substance meets its specification - should also be addressed. For biotechnology-
203 derived products, final drug product testing or additional drug substance stability studies
204 may also be necessary to fully evaluate the impact of the change on the product.

205
206 It should be emphasized that the data package that is included in the regulatory submission
207 is only a subset of the entire information required to support the manufacturing
208 chromatography process change. It is expected that the relevant cGMP information
209 (environmental, instrument qualification, etc.) will be executed, appropriately documented,
210 and available for review upon a facilities inspection. For biotechnology-derived products
211 registered in a BLA, some major changes at an existing facility (i.e. those that have a
212 substantial potential to adversely affect the product) may require, under 21 CFR 601.2(d), a
213 satisfactory cGMP compliance status prior to distribution of the product made with the
214 change.

215
216 The responsibility for reporting changes of the type described in this guidance lies with the
217 party that owns the application.

218
219 Although this document is intended to provide guidance on regulatory reporting categories
220 when implementing changes in chromatographic processes inherently it can not be
221 comprehensive enough to cover all specific cases. Multiple factors should be addressed
222 before the company can decide on a most effective and safe path. Key factors to consider
223 when changing manufacturing chromatography systems are listed in appendix A.

224 225 **IV. ASSESSMENT OF CHANGE**

226
227 A holder of an approved application must assess the effects of the change before
228 distributing a drug product made with a manufacturing change (section 506A(b) of the Act,
229 and section 351 of the PHS Act). A central tenet of this guidance is that a given change in
230 the drug substance manufacturing process can be adequately assessed by comparing pre-
231 and post-change materials, and demonstrating that the post-change material is comparable
232 to the pre-change material (i.e. of the same or better quality, as described below). For
233 biologically-derived products, it should be noted that better quality does not always mean
234 "more pure". In certain products the impurities could act as stabilizers, or act to enhance or

235 inhibit the activity of the active ingredients. For example, a more highly pure product
236 (which can also be the case with less pure product) may cause an immunogenic response or
237 product aggregation.
238

239 When comparability cannot be demonstrated solely with chemical and physical testing,
240 applicants should submit a prior approval supplement and should consider appropriate tests
241 for qualification of impurities, assessment of stability and the need to perform PK/PD
242 studies to demonstrate comparability. If physicochemical comparability cannot be
243 demonstrated on the production batch, then the change has a substantial potential to have an
244 adverse effect on the identity, strength, quality, purity, and/or potency of the drug product.
245 An applicant still wishing to institute such a change would be expected to provide
246 additional information in support of the change, such as in-vitro or in-vivo biological
247 studies, or human clinical trials.
248

249 The stability of some drug products can be affected by small changes in impurities (e.g.,
250 increases in the trace levels of heavy metals). For drug products with a potential for
251 stability problems, the first production batch(es) of drug product made with post-change
252 drug substance should be included in the applicant's stability testing program.
253

254 Two major factors for determining comparability in the drug substance are the impurity
255 profile (both product and process related impurities) and physical/structural properties. For
256 the purposes of this guidance, only these factors will be discussed. However, other factors
257 that can be important in individual cases should be evaluated to demonstrate comparability.
258 For example, if the drug substance is defined as a mixture of active analogs, the ratios after
259 the change should be within the stated acceptance criteria, or if not stated, within the upper
260 and lower statistical limits of historical data. For small molecules, the two
261 physical/structural properties of the drug substance, morphic form¹ and particle size, are
262 considered critical for evaluation of comparability, established after the last true solution.
263 In the case of a biological product, materials leading to safety concerns, such as the removal
264 of adventitious agents from the process stream, should also be considered.
265

266 **Comparability of Impurity Profiles**

267

268 The impact of manufacturing modifications on the impurity profile is evaluated by
269 determining levels of existing impurities, and new impurities. It is important to
270 determine the stage in the manufacturing process at which impurities should be
271 evaluated, and to establish the adequacy of the analytical procedures used for this
272 purpose. Process impurities may consist of both small and large molecules. Levels of
273 residual solvents and inorganic substances, resin and filter leachables, detergents, and
274 cell culture media components are examples of small molecules, while host cell
275 proteins and DNA are examples of large molecules, which should be considered
276 during evaluation of the impurity profile.
277

278
279 ¹ For the purposes of this guidance, morphic forms also includes hydrates, solvates and amorphous materials

280 Ideally, impurities should be evaluated in the in-process product immediately
281 following the unit operation step in which the manufacturing modification is made. If
282 it can be shown that the impurity profile of an intermediate material following the
283 modified step is comparable (as defined below), the impurity profile of the drug
284 substance will be considered unaffected by the modification. If comparability cannot
285 be demonstrated immediately following the change, the impurity evaluation can be
286 extended to the next downstream unit operation in-process product, and the evaluation
287 process repeated until the drug substance is reached. Comparability can be
288 demonstrated on any single unit operation in-process product or on the drug
289 substance. For biotechnology-derived products, it is likely that in addition to
290 demonstrating comparability at the unit operation that the final drug substance should
291 be tested in order to demonstrate comparability. If testing is performed on the drug
292 substance, comparability should be established for (1) the product related impurity
293 profile; (2) the physical properties, if relevant to the finished dosage form
294 performance; and 3) removal of process related impurities.

295
296 The FDA recognizes that it may not always be possible to establish comparability
297 prior to or at the final drug substance. For example, adequate analytical procedures
298 may not be available, cannot be developed, or, in some cases historical data may not
299 exist. When it is not feasible to evaluate the impurities profile at a unit operation in-
300 process product step, or when comparability cannot be demonstrated at these process
301 stages, the testing can be carried out on the final drug product (with the appropriate
302 assessment of the reporting category based on potential to adversely impact the
303 product).

304
305 The analytical procedures used to evaluate the change should be adequate for
306 quantitating both existing and new impurities at the recommended levels.
307 Development of new analytical procedures may be called for. When new analytical
308 procedures are developed for this purpose, a summary of validation or verification
309 data should be provided. The same analytical procedure should be used when
310 comparing impurity levels in pre- and post-modification batches.

311 312 **Product and Process Related Substances**

313
314 The level of product-related impurities should be assessed through the side-by-side
315 comparison of post-modification batches to the historical data from representative
316 pre-modification batches and/or reference standard samples. For the purpose of this
317 Guidance for Industry, representative pre-modification batches are production scale
318 batches of drug substance that meet all specification acceptance criteria or production
319 scale batches of a unit operation in-process product that has successfully met all
320 forward processing acceptance criteria for previous process steps. The assessment of
321 impurities should normally be carried out soon after manufacture. However, retained
322 samples can be used for the comparison, provided they have been validated to show
323 no trend toward the level of any impurity significantly increasing/decreasing over
324 time.

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The impurities profile will be considered comparable after a given change if three consecutive post-modification batches of either an isolated intermediate or the drug substance are evaluated and the test data for each batch demonstrate that 1) no new impurity is observed that exceeds the ICH Q3A identification threshold of 0.1%; 2) that the level of each specified or existing impurity does not exceed current specification limits or statistical historical ranges for the particular impurity; and 3) the level of total impurities does not exceed the current specification limits or statistical historical ranges for the sum of impurities. When comparing pre- and post-modification batches both process related and product related impurities should be evaluated. The appropriateness of implementing a 0.1% limit should be assessed in light of the limit being dependent on dose. Lower thresholds may be appropriate, particularly for biotechnology-derived drug substances, based on scientific rationale and level of concern. For example, a change in any single impurity (such as a toxin) could potentially have a large impact on safety and/or efficacy.

Additional principles regarding comparability of impurity profiles are outlined below.

- The batches of the unit operation in-process product or drug substance used for testing should be manufactured using exclusively the material that has been subjected to the change(s) (i.e., without blending with prechange material).
- Raw materials introduced into the process (e.g. new salts, stationary phases) shall be evaluated for potential impact on the impurity profile and product quality, safety and efficacy.
- Changes can be evaluated using data from qualified smaller scale batches representative of the full scale batches provided the FDA deems appropriate experience exists with the manufacturing process. If comparability is demonstrated by, and the filing based on, smaller scale batches, the first production batch should also be evaluated for comparability.
- Each existing impurity shall remain within its stated limit or, if not stated, within the statistical upper and lower limit range of historical data.
- Total impurities shall remain within the stated limit or, if not stated, at or below the upper statistical limit of historical data (with the understanding that for biotechnology-derived products, below the historical impurities level may impact product quality).
- Comparability of the impurity profile can be established by testing an appropriate isolated intermediate following the change or the final drug substance. For biotechnology-derived products, even if comparability can be demonstrated for an isolated intermediate, it may be necessary to test final drug substance.

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- Comparability may be established by combining results from multiple unit operation in-process products collected at different steps downstream of the process change. For example, in a 12 step process, the process impurities may be evaluated at Steps 2 and 8, while product impurities are evaluated at Steps 5 and 9.
 - If impurity profile differences, or other changes in the molecule are observed as a result of the chromatography system change, preclinical studies, including safety and PK studies, may be required. The observed impurity profile differences should be discussed with FDA reviewer(s). Furthermore, observed impurity profile differences may require revalidation of subsequent process steps, including viral clearance evaluation and other clearance studies (e.g., DNA, HCP, Protein A). In some cases, clinical studies may be required (e.g. change in glycosylation pattern if glycosylation has been demonstrated to be a key functional attribute).
 - In addition, it should be noted that the use of pilot scale data to support changes for specified biotechnology-derived products must be justified. Scaled-down processes used to demonstrate removal of adventitious agents must be based on sound scientific principles to ensure the process is representative of the full-scale commercial process.

390 In addition, levels of process residuals (solvents and inorganic substances, buffer
391 components, detergents, cell culture media components) and/or other in-process
392 related small molecules should also be considered during evaluation of the impurity
393 profile.

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- Each existing in-process reagent is within its stated limit or, if not stated, is within the upper and lower statistical limit range of historical data.
 - New residual solvents, in either a unit operation in-process product, or the drug substance, are at or below the levels recommended in the ICH guidance Q3C Impurities: Residual Solvents. A toxicological assessment may be necessary if ICH impurity levels are not met.
 - An assessment of the impact of residual solvents levels on the stability of the drug substance.

406 **Comparability of Physical Properties**

407

408 For specified biotechnology-derived products, the physical properties of the drug
409 substance can be impacted by changes made to the chromatography system. Changes
410 such as column chemistry (mobile and stationary phase) or temperature could
411 potentially modify a biotechnology-derived product. For example, changes to
412 chromatographic resin can affect the levels of product related variants, aggregates
413 and/or glycosylation patterns of the product. Bioassays and/or PK/PD studies may be
414 required for biotechnology-derived products as many physicochemical tests would not

415 be able to accurately detect small changes in the product. Animal testing may be
416 required as in-vitro bioassays may not show potential changes in the product's tertiary
417 structure.

418

419 For small molecule products, in general, the physical properties of the drug substance
420 are not likely to be affected by changes made to the chromatography system.
421 Generally, the only way changes can affect the physical properties of the drug
422 substance is by carryover of new impurities or higher levels of existing impurities into
423 the final drug substance. Although minor differences in the impurity profile at this
424 stage are unlikely to cause physical property modifications to the drug substance, the
425 possibility of such changes in physical properties should be considered.
426 Consequently, physical properties of the drug substance, when they are relevant to
427 finished dosage form performance, should be evaluated unless comparability of the
428 impurity profile can be demonstrated prior to the final solution step (e.g., on the crude
429 drug substance or an earlier unit operation in-process product). Generally, only two
430 physical properties of the drug substance, morphic form¹ and particle size, are
431 considered critical for evaluation of comparability. However, other physical
432 properties may be important in individual cases.

433

434 The physical properties of the drug substance will be considered comparable after a
435 given change if post-modification batches of the final drug substance are compared to
436 representative pre-modification batches and the test data for each batch demonstrate:

437

- 438 • Each existing impurity is within its stated limit or, if not stated, is within the
439 upper and lower limits of historical data.
- 440
- 441 • Total impurities are within the stated limit or, if not stated, are within the upper
442 and lower limits of historical data.

443

444 In addition, for small molecules, the physical properties of drug substance will be
445 considered comparable after a given change if at least three post-modification batches
446 of the drug substance are prepared and the data demonstrate:

447

- 448 • Conformance to established acceptance criteria for morphic form or, where
449 acceptance criteria do not exist, the isolation of the same form or mixture of forms
450 within the range of historical data, and
- 451
- 452 • Conformance to historical particle size distribution profile.

453 **V. TYPES OF CHANGE**

454

455 **Documentation**

456

457 The manufacturing process changes discussed in this section cover all aspects of the
458 chromatography system. The following documentation requirements apply to all changes:

459

460 • Description of the change and rationale for the proposed change and reporting
461 category.

462

463 • A summary of any pertinent variation in equipment, raw materials, or operating
464 conditions.

465

466 • A description and summary of validation or verification data for any new analytical
467 procedure and also for existing procedures if their use is being extended beyond
468 their original purpose. The additional validation/verification data that should be
469 submitted will depend on the individual case and is to be consistent with ICH
470 Guidance (Q2A and Q2B) on method validation.

471

472 • Data to support the evaluation of the impurity profile (both process and product
473 related), physico-chemical properties and changes in product related impurities.
474 Validation or verification data to support that the process will consistently meet in-
475 process acceptance criteria following the change.

476

477 • Data to support the evaluation of drug substance and/or drug product stability
478 consistent with ICH Guidance Q1A and Q5C.

479

480 • Specifications (tests and acceptance criteria) for new reagents and solvents and
481 Certificates of Analysis from suppliers, if applicable. When a new solvent or other
482 raw material or component is introduced into the process, the possibility of
483 carryover into the drug substance should be assessed. When a new resin is
484 introduced for biotechnology-derived products, potential leachables should be
485 assessed.

486

487 • If a move to a new facility, the name and address and other pertinent organizational
488 information for the new facility. For biotechnology-derived products, a list of the
489 products produced in the facility in the same areas and a description of precautions
490 to prevent contamination/cross contamination. If applicable, the date of the last
491 successful FDA inspection of the site for similar type operations.

492

493 **Change Tables**

494

495 The following tables provide guidance on the CMC documentation and regulatory reporting
496 categories for a given chromatography system manufacturing change based on the potential
497 to adversely affect the identity, strength, quality, purity or potency of a product as they
498 relate to the safety or effectiveness of the product. Examples of changes within a category
499 are given. The appropriate reporting category can only be determined using a risked-based
500 approach. The proposed regulatory reporting category for a given example is only
501 appropriate if supported by full array of comparability data test documentation.

502

503 Although the following tables describe the appropriate test documentation and reporting
504 category for an individual change, it is acknowledged that changes to a chromatographic
505 system often involve various combinations of individual changes. For example, a site
506 change may also involve column equipment and manufacturing process changes or a
507 component and composition change may necessitate a column scale-up change. For
508 multiple related changes where the recommended reporting categories for the individual
509 changes differ, it is recommended that the filing be in accordance with the most restrictive
510 of those recommended for the individual changes. When the multiple related changes all
511 have the same recommended reporting category, it is recommended that the filing be in
512 accordance with the reporting category for the individual changes. However, an assessment
513 on the potential impact to the product due to the cumulative affect of the multiple changes
514 should be performed to determine if a higher reporting category is warranted (e.g. multiple
515 CBE-30 changes bundled together and with the reporting category bumped up to a Prior
516 Approval Supplement).

517

518 Changes are categorized into three levels

519

- 520 • Minimal changes are those that FDA has identified as having a minimal potential
521 to adversely affect the identity, strength, quality, purity, or potency of a product
522 as they relate to the safety or effectiveness of the product. These changes are
523 reported in an Annual Report.
- 524
- 525 • Moderate changes are those that FDA has identified as having a moderate
526 potential to adversely affect the identity, strength, quality, purity, or potency of a
527 product as they relate to the safety or effectiveness of the product. These changes
528 are reported either as CBE or CBE-30 Supplements.
- 529
- 530 • Substantial changes are those that FDA has identified as having a substantial
531 potential to adversely affect the identity, strength, quality, purity, or potency of a
532 product as they relate to the safety or effectiveness of the product. These
533 changes are reported as Prior Approval Supplements.

534 **1. MOBILE PHASE**

535

536 This section of the guidance focuses on changes in the concentration of reagents or a change in the components and/or composition of
 537 reagents used in the mobile phase.

538

539 A. Small Molecules

540

Change	Examples	Test Documentation	Reporting Category
Minimal Potential	Change in the buffer concentration (e.g. 0.1M to 0.2M phosphate buffer).	Application/compendial release requirements. Additional data to support the change as appropriate.	Annual Report
Moderate Potential	Change in the elution buffer pH. Change in the slope for a gradient system (e.g. 40 minutes to 30 minutes to reach 50% Buffer B) that alters the peak elution times. Change in the type of salt used (e.g. ammonium chloride to sodium phosphate). Change in organic constituent of the mobile phase (e.g. acetonitrile to methanol).	Application/compendial release requirements. Specifications for new reagents or solvents, if applicable. Data on up to three consecutive batches made using the new mobile phase, historical data for comparison, and a description of the source of the historical data. Additional characterization data as needed to show comparability and appropriate supportive historical development studies to demonstrate no adverse impact of change on drug substance.	Before and including the final intermediate step: Annual Report After the final intermediate step: CBE-0 Supplement.
Substantial Potential	None Identified		

541 B. Specified Biotechnology-Derived Products

Change	Examples	Test Documentation	Reporting Category
Minimal Potential	<p>Change in solvent or salt manufacturer.</p> <p>Change in the pH or salt concentration for a wash or regeneration step.</p>	<p>Application/compendial release requirements.</p> <p>Additional data to support the change as appropriate. Assessment of no impact on column lifetimes, carry-over of impurities or impact on viral clearance. Revalidation of virus or adventitious agent removal or inactivation if current removal factor is decreased by change.</p>	Annual Report
Moderate Potential	<p>Change in the elution buffer concentration (e.g. 0.1 M to 0.2M phosphate buffer).</p> <p>Change in the elution buffer pH.</p> <p>Change in the type of salt used (e.g. sodium chloride to sodium acetate).</p> <p>Change in the elution condition (e.g. slope for a gradient system) that alters the peak elution times.</p> <p>Changes in organic constituent of the mobile phase (e.g. acetonitrile to methanol).</p>	<p>Application/compendial release requirements.</p> <p>Assessment of no impact on column lifetimes, carry-over of impurities or impact on viral clearance. Revalidation of virus or adventitious agent removal or inactivation if current removal factor is decreased by change (based on nature or source of new salt or solvent).</p> <p>Data on up to three consecutive batches made using the new mobile phase, historical data for comparison, and a description of the source of the historical data. Additional characterization data as needed to show comparability and appropriate supportive historical development studies to demonstrate no adverse impact of change on drug substance.</p> <p>Stability Testing: <u>Significant body of information available:</u> One batch with three months accelerated stability data reported in supplement; one batch on long-term stability, data reported in annual report.</p> <p><u>Significant body of information not available:</u> Up to three batches with three months accelerated stability data reported in supplement; one batch on long-term stability, data reported in annual report.</p>	CBE-0/CBE-30 Supplement. Long term stability data reported in AR
Substantial Potential	None Identified		

542 **2. STATIONARY PHASE**

543

544 This section of the guidance focuses on changes in the components and composition of the stationary phase.

545

546 **A. Small Molecules**

547

Change	Examples	Test documentation	Reporting Category
Minimal Potential	Change in solid support parameters (e.g. pore size, particle size, etc.).	Application/compendial release requirements. Additional data to support the change as appropriate (e.g. vendor's support files).	Annual Report
Moderate Potential	Change in composition of the solid support (silica to polymer based). Change in the ligand spacer arm of the bonded phase but keeping the same basic separation mode (e.g. C18 to C8 on a silica support). Change in the chemical nature of the bound ligand (e.g. cyano to an octadecyl resin).	Application/compendial release requirements. Data on up to three consecutive batches made using the new stationary phase, historical data for comparison, and a description of the source of the historical data. Additional characterization data as needed to show comparability and appropriate supportive historical development studies to demonstrate no adverse impact of change on drug substance. Additional data to support the change as appropriate (i.e. evaluation on potential leaches)	Before and including the final intermediate step: Annual Report After the final intermediate step: CBE-0 Supplement.
Substantial Potential	None Identified		

548 B. Specified Biotechnology-Derived Products

Change	Examples	Test Documentation	Reporting Category
Minimal Potential	Change in solid support parameters (e.g. pore size, particle size, etc.) that does not affect mode of separation.	Application/compendial release requirements Additional data to support the change as appropriate. Assessment of no impact on column lifetimes, carry-over of impurities or impact on viral clearance. Revalidation of virus or adventitious agent removal or inactivation if current removal factor is decreased by change.	Annual Report
Moderate Potential	<p>Change in the method of manufacture of the ligand. No change in the ligand or coupling chemistry (e.g. manufacture change to remove animal sourced materials for an affinity resin).</p> <p>Change in the manufacturer of the packing material.</p> <p>Change in composition of the solid support (e.g. silica to polymer based).</p> <p>Change in the chemical nature of the bound ligand (e.g. cyano to octadecyl resin).</p>	<p>Application/compendial release requirements.</p> <p>Evaluation of leachables, capacity and yield. Additional data to support the change as appropriate (e.g. vendor's support files). Prospective or concurrent resin lifetime studies to level of previously used resin. Assessment of no impact on carry-over of impurities or impact on viral clearance. Revalidation of virus or adventitious agent removal or inactivation if current studies are invalidated by change (based on nature or source of new solid support or ligand).</p> <p>Data on up to three consecutive batches made using the new stationary phase, historical data for comparison, and a description of the source of the historical data. Additional characterization data as needed to show comparability and appropriate supportive historical development studies to demonstrate no adverse impact of change on drug substance.</p> <p>Stability Testing: <u>Significant body of information available:</u> One batch with three months accelerated stability data reported in supplement; one batch on long-term stability, data reported in annual report. <u>Significant body of information not available:</u> Up to three batches with three months accelerated stability data reported in supplement; one batch on long-term stability, data reported in annual report.</p>	CBE-0/CBE-30 Supplement. Long-term stability data reported in AR.
Substantial Potential	None Identified		

549 **3. CHROMATOGRAPHIC CONDITIONS**

550
 551 This section of the guidance focuses on changes in the components and parameters in chromatographic conditions (e.g. temperature,
 552 pH, reagent stoichiometry, time, collection criteria, and column lifetime).

553
 554 A. Small Molecules

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Change	Examples	Test Documentation	Reporting Category
Minimal Potential	<p>Changes in column cleaning and/or regeneration (e.g. additional washing or equilibration step, change in regeneration buffer composition).</p> <p>Changes in column storage conditions (e.g. storage at pH 4 instead of pH 7) within resin manufacturer's stability specifications.</p> <p>Changes in column operational temperature.</p> <p>Changes in linear mobile phase flow rate (e.g. from 50 cm/hr to 100 cm/hr) in other phases than the elution phase.</p> <p>Extended column lifetime supported by body of historic data including evaluation of impurity profile, carry-over, physical characteristics (e.g. back pressure).</p>	<p>Application/compendial release requirements.</p> <p>Additional data to support the change as appropriate (e.g. impact of storage conditions on resin lifetimes).</p>	Annual Report
Moderate Potential	<p>Increase in column loading (e.g. from 8 gm/ L of resin by reversed-phase HPLC to 12 gm/ L).</p> <p>Changes in linear mobile phase flow rate (e.g. from 50 cm/hr to 100 cm/hr) in the elution phase.</p> <p>Changes in load composition (e.g. pH, conductivity, solvent composition and product</p>	<p>Application/compendial release requirements.</p> <p>Data on up to three consecutive batches made using the new chromatographic conditions, historical data for comparison, and a description of the source of the historical data.</p> <p>Additional characterization data as needed to show comparability and appropriate supportive historical development studies to demonstrate no adverse impact of change on drug substance.</p>	<p>Before and including the final intermediate step: Annual Report</p> <p>After the final intermediate step: CBE-0 Supplement.</p>

	concentration). Changes in collection criteria resulting in a higher pool volume or shift in collection window. Changes in holding time or temperature for intermediates. Changes of in-process program (e.g. deletion of a process control or an analytical method).		
Substantial Potential	None Identified		

556 B. Specified Biotechnology-Derived Products
 557

Change	Examples	Test Documentation	Reporting Category
Minimal Potential	<p>Changes in column cleaning and/or regeneration (e.g. additional washing or equilibration step, change in regeneration buffer composition) with assessment of no impact on carry-over of impurities and viral clearance.</p> <p>Changes in column storage conditions (e.g. storage at pH 4 instead of pH 7) within resin manufacturer's stability specifications.</p> <p>Extended column lifetime supported by body of historic data including evaluation of impurity profile, carry-over, physical characteristics (e.g. back pressure).</p>	<p>Application/compendial release requirements.</p> <p>Additional data to support the change as appropriate (e.g. impact of storage conditions or regeneration buffer on resin lifetime). Assessment of no impact on column lifetime, carry-over of impurities or impact on viral clearance. Revalidation of virus or adventitious agent removal or inactivation if current studies are invalidated by change.</p>	Annual Report
Moderate Potential	<p>Changes in flow rate (e.g. from 50 cm/hr to 100 cm/hr) for the elution, cleaning and/or regeneration phase with assessment of no impact on carry-over of impurities and viral clearance.</p> <p>Changes in column operational temperature.</p> <p>Changes in load composition (e.g. pH, conductivity and product concentration).</p> <p>Changes in collection criteria resulting in a higher pool volume or shift in collection window.</p> <p>Increase in column loading (e.g. from 8 gm/L of resin by reversed-phase HPLC to 12 gm/L).</p>	<p>Application/compendial release requirements.</p> <p>Revalidation of lifetimes of resin might be required to demonstrate that the increased load does not adversely impact the ability of the resin to clear impurities over its lifetime.</p> <p>Assessment of no impact on carry-over of impurities or impact on viral clearance. Revalidation of virus or adventitious agent removal or inactivation if current studies are invalidated by change (based on source and raw materials).</p> <p>Data on up to three consecutive batches made using the new chromatographic conditions, historical data for comparison, and a description of the source of the historical data. Additional characterization data as needed to show comparability and appropriate supportive historical development studies to demonstrate no adverse impact of</p>	CBE-0/CBE-30 Supplement. Long-term stability data reported in AR.

	<p>Changes in holding time or temperature for intermediates.</p> <p>Changes of in-process program (e.g. deletion of a process control or an analytical method).</p>	<p>change on drug substance.</p> <p>Stability Testing: <u>Significant body of information available:</u> One batch with three months accelerated stability data reported in supplement; one batch on long-term stability, data reported in AR.</p> <p><u>Significant body of information not available:</u> Up to three batches with three months accelerated stability data reported in supplement; one batch on long-term stability, data reported in AR.</p>	
Substantial Potential	None Identified		

558 **4. EQUIPMENT**

559
 560 This section of the guidance focuses on changes in the chromatography system, both in design and composition.

561
 562 A. Small Molecules

563
 564 A change to new equipment that is not significantly different from that previously used, with no modifications to process parameters,
 565 need not be filed with the Agency, and equivalence testing as described in this document need not be carried out. However,
 566 installation qualification and operational qualification information should be retained in-house and is subject to FDA's review at its
 567 discretion.
 568

Change	Examples	Test documentation	Reporting Category
Minimal Potential	None Identified		
Moderate Potential	After the final intermediate step: New equipment is significantly different from that previously used (e.g. switching from glass to metal columns).	Application/compendial release requirements. Data on up to three consecutive batches made using the new equipment, historical data for comparison, and a description of the source of the historical data. Additional characterization data as needed to show comparability and appropriate supportive historical development studies to demonstrate no adverse impact of change on drug substance.	CBE-0 Supplement.
Substantial Potential	None Identified		

569 B. Specified Biotechnology-Derived Products
 570

Change	Examples	Test Documentation	Reporting Category
Minimal Potential	<p>Change or addition of alternative equipment of the same scale, design and operating principles. ("like-for-like" change, all wetted materials as currently specified in application) listed as major equipment in the registration.</p> <p>Change in wetted component material (e.g. from fixed stainless steel tanks to plastic bags for buffers, from stainless steel to polymer frits, from different elastomer for seals or glass to stainless steel column (all wetted materials characterized/currently used in process).</p> <p>Modification of chromatography equipment intended only to improve column/packing performance (improvements of flow distributors or change from standard column to pack-in-place column with no new materials of construction).</p>	<p>Application/compendial release requirements.</p> <p>Additional data to support the change as appropriate (e.g. moving from glass to stainless steel an assessment of corrosion using high salt concentration; evaluation of potential leaches).</p>	Annual Report

<p>Moderate Potential</p>	<p>Replacement of column equipment with that of similar, but not identical, design and operating principle.</p> <p>Change from non-automated or non-mechanical equipment to automated or mechanical equipment.</p>	<p>Application/compendial release requirements. Assessment of no impact on carry-over of impurities or impact on viral clearance. Revalidation of virus or adventitious agent removal or inactivation if current studies are invalidated by change.</p> <p>Data on up to three consecutive batches made using the new equipment, historical data for comparison, and a description of the source of the historical data. Additional characterization data as needed to show comparability and supportive historical development studies to demonstrate no adverse impact of change on drug substance. Revalidation of process step may be considered.</p> <p>One batch on long-term stability, data reported in AR.</p>	<p>CBE-0/CBE-30 Supplement. Long-term stability reported in AR</p>
<p>Substantial Potential</p>	<p>Replacement of column equipment which operate with a different operating principle (e.g. packed bed to expanded bed).</p>	<p>Application/compendial release requirements.</p> <p>Assessment of no impact on carry-over of impurities or impact on viral clearance. Revalidation of virus or adventitious agent removal or inactivation if current studies are invalidated by change.</p> <p>Data on up to three consecutive batches made using the new equipment, historical data for comparison, and a description of the source of the historical data. Additional characterization data as needed to show comparability and supportive historical development studies to demonstrate no adverse impact of change on drug substance.</p> <p>Stability Testing: <u>Significant body of information available:</u> One batch with three months accelerated stability data reported in supplement; one batch on long-term stability, data reported in AR. <u>Significant body of information not available:</u> Up to three batches with three months accelerated stability data reported in supplement; one batch on long-term stability, data reported in AR.</p>	<p>Prior Approval Supplement Long-term stability reported in AR</p>

571 **5. CHANGES IN COLUMN SIZE (Scale-up/Scale-down)**

572
 573 This section of the guidance focuses on changes to the size of columns used in the manufacturing process. Post-approval changes in
 574 the size of the column to larger or smaller production columns call for submission of additional information in the application.

575
 576 A. Small Molecules

577
 578 Many scale changes need not be filed with the Agency, and equivalence testing as described in this document need not be carried out.
 579 However, installation qualification and operational qualification information should be retained in-house and is subject to FDA's
 580 review at its discretion.

581

Change	Examples	Test documentation	Reporting Category
Minimal Potential	Before the final intermediate step: Change in column size (e.g. an increase in column diameter from 45 cm to 60 cm). Equipment of a different capacity may be used in conjunction with these changes.	Application/compendial release requirements. Additional data to support the change as appropriate.	Annual Report
Moderate Potential	After the final intermediate step: Change in column size (e.g. an increase in column diameter from 45 to 60 cm). Equipment of a different capacity may be used in conjunction with these changes.	Application/compendial release requirements. Data on up to three consecutive batches made using the new column(s), historical data for comparison, and a description of the source of the historical data. Additional characterization data as needed to show comparability and supportive historical development studies to demonstrate no adverse impact of change on drug substance.	CBE-0 Supplement.
Substantial Potential	None Identified		

582 B. Specified Biotechnology-Derived Products
 583

Change	Examples	Testing Documentation	Reporting Category
Minimal Potential	None Identified		
Moderate Potential	<p>Increased/decreased column diameter (fold increase not important) maintaining same bed height. Assuming proportional load and wash volumes remain constant, also pooling parameters remaining constant.</p>	<p>Application/compendial release requirements.</p> <p>Assessment of no impact on carry-over of impurities or impact on viral clearance. Revalidation of virus or adventitious agent removal or inactivation if current studies are invalidated by change. Assessment of the need to perform/not perform revalidation of the process step.</p> <p>Data on up to three consecutive batches made using the new column(s), historical data for comparison, and a description of the source of the historical data. Additional characterization data as needed to show comparability and supportive historical development studies to demonstrate no adverse impact of change on drug substance.</p> <p>One batch on long-term stability, data reported in AR.</p>	<p>CBE-0/CBE-30 Supplement. Long-term stability data reported in AR.</p>

<p>Substantial Potential</p>	<p>Increased/decreased column size – changing bed height and column diameter and/or making changes to the load or washes to the column.</p>	<p>Application/compendial release requirements.</p> <p>Assessment of no impact on carry-over of impurities or impact on viral clearance. Revalidation of virus or adventitious agent removal or inactivation if current studies are invalidated by change. Revalidation of the column lifetimes and process required as the proportions of load and washes are changing, or the bed height is different.</p> <p>Data on up to three consecutive batches made using the new column(s), historical data for comparison, and a description of the source of the historical data. Additional characterization data as needed to show comparability and supportive historical development studies to demonstrate no adverse impact of change on drug substance.</p> <p>Stability Testing: <u>Significant body of information available:</u> One batch with three months accelerated stability data reported in supplement; one batch on long-term stability, data reported in AR.</p> <p><u>Significant body of information not available:</u> Up to three batches with three months accelerated stability data reported in supplement; one batch on long-term stability, data reported in AR.</p>	<p>Prior Approval Supplement. Long-term stability data reported in AR.</p>
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584 **6. ADDITION/SUBTRACTION OF COLUMN(S)**

585
 586 This section of the guidance focuses on changes in the number of columns used at a particular process step, and on the addition,
 587 substitution or elimination of a chromatography step. These changes call for submission of additional information in the application.
 588

589 A. Small Molecules

590

Change	Examples	Test Documentation	Reporting Category
Minimal Potential	None Identified		
Moderate Potential	Change in the manufacturing process to 1) remove an existing chromatography step, 2) add an additional chromatography step or 3) substitute an existing non-chromatography step with a new chromatography step.	Application/compendial release requirements. Data on up to three consecutive batches made using the new column(s), historical data for comparison, and a description of the source of the historical data. Additional characterization data as needed to show comparability and supportive historical development studies to demonstrate no adverse impact of change on drug substance.	Before the final intermediate step: Annual Report At the final intermediate step: CBE-0 Supplement. After the final intermediate step: CBE-30 Supplement.
Substantial Potential	None Identified		

591 B. Specified Biotechnology-Derived Products
 592

Change	Examples	Test documentation	Reporting Category
Minimal Potential		None Identified	
Moderate Potential	Addition or reduction in number of purification columns used for a unit operation to achieve a change in purification scale not associated with a process change.	Application/compendial release requirements. Assessment of no impact on carry-over of impurities or impact on viral clearance. Revalidation of virus or adventitious agent removal or inactivation if current studies are invalidated by change. Data on up to three consecutive batches made with addition or subtraction of the column(s), historical data for comparison, and a description of the source of the historical data. Additional characterization data as needed to show comparability and supportive historical development studies to demonstrate no adverse impact of change on drug substance. One batch on long term stability, data reported in AR.	CBE-30 Supplement. Long-term stability data reported in AR.

<p>Substantial Potential</p>	<p>Change in the manufacturing process to 1) remove an existing chromatography step, 2) add an additional chromatography step or 3) substitute an existing non-chromatography step with a new chromatography step.</p>	<p>Application/compendial release requirements.</p> <p>Assessment of the need to perform/not perform revalidation of the process step and subsequent downstream steps to demonstrate no impact on product. Assessment of no impact on carry-over of impurities or impact on viral clearance. Revalidation of virus or adventitious agent removal or inactivation if current studies are invalidated by change.</p> <p>Data on three consecutive batches made using with either the addition or subtraction the column(s), historical data for comparison, and a description of the source of the historical data. Additional characterization data as needed to show comparability and supportive historical development studies to demonstrate no adverse impact of change on drug substance.</p> <p>Stability testing: <u>Significant body of information available</u> One batch with three months accelerated stability data reported in supplement; one batch on long-term stability, data reported in Annual Report</p> <p><u>Significant body of information not available.</u> Three batches with three months accelerated stability data reported in supplement; one batch on long-term stability, data reported in Annual Report.</p>	<p>Prior Approval Supplement. Long-term stability data reported in AR.</p>
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594 **7. SITE CHANGES**

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596 Site changes include changes in location of the site of manufacture of intermediates and the drug substance for both company-owned
 597 and contract manufacturing facilities. Site changes can involve the addition of new facilities or the relocation of manufacturing
 598 facilities approved in the referenced application(s). The term “No changes in equipment” is meant to encompass both the same
 599 equipment being moved from one facility to another or new equivalent equipment being purchased and placed in a new facility.
 600 Transfer of an existing manufacturing step to a facility approved for other manufacturing steps should be considered a site change.
 601 Equipment changes (Section IV.4.) may often accompany a site change and should be considered under multiple related changes
 602 (Section IV.8.) with the filing moving to the most restrictive of those individual changes. Cross contamination should be considered
 603 when the site change results in the product moving into a facility already manufacturing product, with an awareness of the increased
 604 potential for adverse impact when moving from a single to a multi-product facilities. Any changes in the site of manufacture that are
 605 not prior approval supplements can only fit this category if a recent (last 2 years) acceptable cGMP inspection for the type of operation
 606 involved has occurred. Any site change requiring a pre-approval inspection will need to be reported as a PAS with the exception of
 607 small molecule drug substance intermediates.

608

609 **A. Small Molecules**

610

611 Site changes within a single facility need not be filed with the Agency, and equivalence testing as described in this document need not
 612 be carried out. However, installation qualification and operational qualification information should be retained in-house and is subject
 613 to FDA’s review at its discretion.

614

Change	Examples	Test documentation	Reporting Category
Minimal Potential	A move of a chromatographic step to a different manufacturing site for drug substance intermediates, prior to the final intermediate.	Application/compendial release requirements. Concise description of the manufacturing steps being transferred, a summary (with justification) of any pertinent variation in equipment or process. Certificate of Analysis from the manufacturer for each outsourced intermediate affected by the site change.	Annual Report

<p>Moderate Potential</p>	<p>A move to a different manufacturing site within the same company outside of the current manufacturing campus (different central file number).</p> <p>A move to a new site owned by a contract manufacturer not previously approved for the chromatography step(s) being transferred.</p> <p>A restart at the previous manufacturing site for the type of operation that has been discontinued for at least two years.</p>	<p>Application/compendial release requirements.</p> <p>Concise description of the manufacturing steps being transferred, a summary (with justification) of any pertinent variation in equipment or process. The new site should have similar environmental controls (e.g., temperature, humidity, cross contamination).</p> <p>Data on at least three consecutive batches made at the new site, historical data for comparison, and a description of the source of the historical data. Additional characterization data as needed to show comparability and supportive historical development studies to demonstrate no adverse impact of change on drug substance.</p> <p>Certificate of Analysis from the manufacturer for each outsourced intermediate affected by the site change.</p>	<p>Prior to and including the final intermediate step: CBE-0 Supplement After the final intermediate step: CBE-30 Supplement</p>
<p>Substantial Potential</p>	<p>A move to a different manufacturing site when the site does not have a satisfactory cGMP inspection for the type of operation that is being moved. Does not apply to intermediates.</p>	<p>Application/compendial release requirements</p> <p>Concise description of the manufacturing steps being transferred, a summary (with justification) of any pertinent variation in equipment or process. The new site should have similar environmental controls (e.g., temperature, humidity, cross contamination).</p> <p>Data on at least three consecutive batches made at the new site, historical data for comparison, and a description of the source of the historical data. Additional characterization data as needed to show comparability and supportive historical development studies to demonstrate no adverse impact of change on drug substance.</p> <p>Certificate of Analysis from the manufacturer for each outsourced intermediate affected by the site change.</p>	<p>Prior Approval Supplement.</p>

615 B. Specified Biotechnology-Derived Products
 616

Change	Examples	Test Documentation	Reporting Category
Minimal Potential	<p>A move of a chromatography system from the first floor of a building to the second floor of the building.</p> <p>A move of a chromatography system from one building to another building within the same campus with no changes to the equipment, or other operating parameters (i.e. same skids etc).</p>	<p>Application/compedial release requirements.</p> <p>Concise description of the manufacturing steps being transferred, a summary (with justification) of any pertinent variation in equipment or process.</p> <p>List of other products made in the area if multi-product facility addressing the potential for contamination/cross contamination or exposure to other processes that could change the status of the adventitious agent concerns.</p>	Annual Report
Moderate Potential	<p>A move to a different manufacturing site within the same company outside of the current manufacturing campus (different central file number) with assessment of no impact on viral clearance.</p> <p>A move to a new site owned by a contract manufacturer not previously approved for the chromatography step(s) being transferred.</p> <p>A restart at the previous manufacturing site for the type of operation that has been discontinued for at least two years.</p>	<p>Application/compedial release requirements.</p> <p>Concise description of the manufacturing steps being transferred, a summary (with justification) of any pertinent variation in equipment or process.</p> <p>List of products produced in the facility in the same areas if a multi-product facility and description of precautions to prevent contamination /cross contamination. Identical but new equipment, and identical operating and process parameters should apply. The new site should have similar type of environmental controls (e.g., temperature, humidity, cross contamination).</p> <p>Data on up to three consecutive batches made at the new site, historical data for comparison and a description of the source of any historical data. Additional characterization data as needed to show comparability and appropriate supportive historical development studies to demonstrate no adverse impact of change on drug substance.</p> <p>Stability Testing: Up to three months of stability data on the first batch, and a commitment to three batches of DS on long-term stability, and one batch of DP made from the DS.</p>	CBE 30 Supplement. Long-term stability data reported in AR.

<p>Substantial Potential</p>	<p>A move to a different manufacturing site when the new manufacturing site does not have a satisfactory cGMP inspection for the type of operation that is being moved.</p>	<p>Application/compendial release requirements.</p> <p>Concise description of the manufacturing steps being transferred, a summary (with justification) of any pertinent variation in equipment or process.</p> <p>List of products produced in the facility in the same areas if a multi-product facility, simple floor plan, description of precautions to prevent contamination/cross contamination. The new site should have similar type of environmental controls (e.g., temperature, humidity, cross contamination). If contract manufacturer, reference to a written agreement for contract manufacturer and responsibilities of each party.</p> <p>Data on up to three consecutive batches made at the new site, and comparison of the DS from the new site to previously manufactured DS, with additional characterization data as needed to show comparability, and a description of the source of the historical data.</p> <p>Stability Testing: <u>Significant body of information available:</u> One batch with three months accelerated stability data reported in supplement; one batch on long-term stability, data reported in annual report.</p> <p><u>Significant body of information not available:</u> Up to three batches with three months accelerated stability data reported in supplement; one batch on long-term stability, data reported in annual report.</p>	<p>Prior Approval Supplement. Long-term stability data reported in AR.</p>
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617 **8. MULTIPLE RELATED CHANGES**

618

619 Multiple related changes involve various combinations of individual changes. For example,
620 a site change may also involve column equipment and manufacturing process changes or a
621 component and composition change may necessitate a column scale-up change. For
622 multiple related changes where the recommended reporting categories for the individual
623 changes differ, it is recommended that the filing be in accordance with the most restrictive
624 of those recommended for the individual changes. When the multiple related changes all
625 have the same recommended reporting category, it is recommended that the filing be in
626 accordance with the reporting category for the individual changes, with an assessment of the
627 impact of the multiple changes. The cumulative effect of multiple changes should be
628 determined not to increase the risk of an adverse effect on the product.

629

630 **VI. REFERENCES**

631

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658 J. "Guidance for Industry – Comparability Protocols – Chemistry, Manufacturing and
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661 K. "Guidance for Industry – Comparability Protocols – Protein Drug Products and
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665 L. ICH Q1A. Stability Testing of New Drugs and Products

666 M. ICH Q6A. Specifications: Test Procedures and Acceptance Criteria for
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668 N. ICH Q6B. Specifications: Test Procedures and Acceptance Criteria for New Drug
669 Substances and New Drug Products: Chemical Substances

670 O. ICH Q7A. Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients

671 **APPENDIX A**

672

673 **Factors to Consider When Changing Chromatographic Systems**

674

- 675 1. What is the modality of the separation (e.g. reversed-phase, size –exclusion, ion-
676 exchange, etc.)?
- 677 2. What does the separation accomplish in the process (e.g., removal of product variants,
678 reactants, host proteins, process residuals, adventitious agents, etc.)?
- 679 3. What is the mechanism of action and how will this be impacted by the change?
- 680 4. Can the available assays adequately assess the impact of the change on the intermediate
681 or drug substance? With statistical significance?
- 682 5. Will the change impact any downstream step? If so, include this in the assessment.
- 683 6. Are the tools to assess comparability up to the job (i.e., matched to the complexity of
684 the drug substance)?
- 685 7. Will the change impact the stability of the intermediate, drug substance or drug product
686 or the validity of the reported stability studies?
- 687 8. How will the change impact the robustness or/and the reproducibility of the process?
- 688 9. Does the quality and quantity of the data support the assessment of how the change can
689 affect the quality and properties of intermediate products, drug substance or drug
690 product?
- 691 10. Does a risk – benefit analysis support making the change?
- 692 11. What is the impact on microbial control in the process (e.g. bacterial/fungal growth and
693 the capability of the process on endotoxin removal)? What is the impact of the change
694 on validation of removal of specific impurities such as endotoxin?
- 695 12. Is the change within or outside the range of previously reported data (e.g. a parameter
696 changed from one value to another value should be compared to the validated range)?
- 697 13. What affect will the change have on the validity of previous virus or adventitious agent
698 removal or inactivation validation studies?
- 699 14. What effect will the change have on the processing times? Will the time increase?
700 What is the impact of this on the risk of an adverse effect?
- 701 15. What effect will the change have on potential for contamination or cross contamination
702 of the product?
- 703 16. What are the immunogenic consequences of the change (based on structural analysis
704 and content of di- and polymeric aggregates)?

705 **APPENDIX B**

706

707 **Active Pharmaceutical Ingredient Characterization Tests**

708

709 Information from specific tests regarding identity, purity, stability and consistency of
710 manufacture of the drug substance should be provided.

711

712 Examples of analyses for which information may be submitted for specified biotechnology-
713 derived products include, but are not necessarily limited to the following:

- 714 • Amino acid analysis
- 715 • Amino acid sequencing, entire sequence or amino- and carboxy-terminal sequences
- 716 • Peptide mapping
- 717 • Determination of disulfide linkage
- 718 • Sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE)
- 719 • Isoelectric focusing
- 720 • Conventional and high-pressure liquid chromatography (HPLC) e.g. reversed-phase,
721 size exclusion, ion-exchange, etc.
- 722 • Mass spectrometry
- 723 • Carbohydrate Analysis
- 724 • Assays to detect product related proteins including deamidated, oxidized, cleaved, and
725 aggregated forms and other variants e.g., amino acid substitutions, adducts/derivatives.
- 726 • Assays to detect residual host proteins, DNA, reagents
- 727 • Immunochemical analyses
- 728 • Assays to quantitate bioburden and endotoxin

729

730 Examples of analyses for which information may be submitted for small molecules include,
731 but are not necessarily limited to the following:

- 732 • High Performance Liquid Chromatography (reversed phase, chiral)
- 733 • Gas Chromatography
- 734 • X-Ray
- 735 • Laser diffraction (particle size analysis)

736 **APPENDIX C: GLOSSARY**

737

738 **Acceptance Criteria:** Numerical limits, ranges, or other criteria for the test described.

739

740 **Assess the Effects of the Change:** To evaluate the effects of a manufacturing change on the
741 identity, strength, quality, purity, and potency of a drug product as those factors may relate to the
742 safety or effectiveness of the drug product.

743

744 **Batch:** A specific quantity of a drug or other material that is intended to have uniform character
745 and quality, within specified acceptance criteria, and is produced according to a single
746 manufacturing order during the same cycle of manufacture (21 CFR 210.3(b)(2))

747

748 **Biological Tests:** Biological tests include animal, cell culture or biochemical based testing that
749 measures a biological, biochemical or physiological response.

750

751 **Critical:** Describes a process step, process condition, test requirement, or other relevant parameter
752 or item that must be controlled within predetermined criteria to ensure that the drug substance meets
753 its specification.

754

755 **Comparability:** The quality or state of being suitable for comparison. FDA may determine that
756 two products are comparable if the results of the comparability testing demonstrate that a
757 manufacturing change does not affect identity, strength, quality, purity or potency as they may relate
758 to the safety or effectiveness of the product.

759

760 **Comparability Protocol:** A protocol submitted by an applicant under CFR 601.12(e) and 314.70
761 (g)(4) that describes the specific tests and validation studies and acceptable limits to be achieved to
762 demonstrate the lack of adverse effect for specified types of manufacturing changes on the identity,
763 strength, quality, purity and potency of the product as they may relate to the safety or effectiveness
764 of the product. Any such protocols, or change to a protocol, shall be submitted as a supplement
765 requiring approval from FDA prior to distribution of the product which, if approved, may justify a
766 reduced reporting category for the particular change because the use of the protocol for that type of
767 change reduces the potential risk of an adverse effect.

768

769 **Contiguous Campus:** Continuous or unbroken site or a set of buildings in adjacent city blocks.

770

771 **Drug Product:** A finished dosage form (e.g., tablet, capsule, or solution) that contains a drug
772 substance, generally, but not necessarily, in association with one or more other ingredients (21 CFR
773 314.3(b)).

774

775 **Drug Substance:** An active ingredient that is intended to furnish pharmacological activity or other
776 direct effect in the diagnosis, cure, mitigation, treatment, or prevention of a disease, or to affect the
777 structure or any function of the human body, but does not include intermediates used in the
778 synthesis of such ingredient (21 CFR 314.3(b)).

779

780 **Equipment:** Automated or non-automated, mechanical or non-mechanical equipment
781 used to produce the drug product, including equipment used to package the drug product.

782

783 **Equivalence:** See comparability

784

- 785 **Facility:** A physical building with a defined building number or name.
786
- 787 **Formulation:** A listing of the ingredients and composition of the dosage form.
788
- 789 **Historical Data:** For purposes of this guidance, data on impurities or physical attributes from three
790 or more consecutive representative premodification batches. The upper statistical limit of an
791 impurity should be based on the mean plus three times the standard deviation. A lower statistical
792 limit can be similarly defined, where appropriate (e.g., the level of an active component, moisture
793 content).
794
- 795 **Impurity:** Any component of the drug substance that is not the chemical entity defined as the drug
796 substance or an excipient in the drug product (ICH Q6A).
797
- 798 **Impurity profile:** A description of the identified and unidentified impurities present in a drug
799 substance (ICH A3A).
800
- 801 **In-process Material:** Any material fabricated, compounded, blended, or derived by chemical
802 reaction that is produced for, and used in, the preparation of the drug product (21 CFR 210.3(b)(9))
803
- 804 **Intermediate Material:** The chemical mixture that may or may not have completed the chemistry
805 steps, and thus is not in its final chemical and physical/conformational state, and has not been
806 through final process steps to final drug substance. Examples in the small molecule world include
807 isolated intermediates, intermediates and final intermediates. Examples in the large molecule world
808 include **Crude Protein Mixtures** (pre transformation, conversion or folding) and purified protein
809 prior to any final polishing steps.
810
- 811 **Isolated Intermediate:** An intermediate that is obtained as the product after workup of a
812 purification step in the process scheme for the drug substance. The isolation or purification
813 procedure should be part of the validated process. An aliquot of a product that is worked up and/or
814 purified for purposes of characterization does not constitute an isolated intermediate.
815
- 816 **Justification:** Reports containing scientific data and expert professional judgment to substantiate
817 decisions.
818
- 819 **Operating Principle:** Rules or concepts governing the operation of the system.
820
- 821 **Pilot Scale:** The manufacture of a drug substance by a procedure fully representative of and
822 simulating that to be applied to a production scale batch.
823
- 824 **Process:** A series of operations and/or actions used to produce a desired result.
825
- 826 **Range:** The extent to which or the limits between which acceptable variation exists.
827
- 828 **Same:** Agreeing in kind, amount; unchanged in character or condition.
829
- 830 **Scale-up:** The process of increasing the column volume.
831
- 832 **Scale-down:** The process of decreasing the column volume.
833

834 **Similar:** Having a general likeness.

835

836 **Significant body of information:** A significant body of information on the stability of the drug
837 product is likely to exist after five years of commercial experience for new molecular entities, or
838 three years of commercial experience for new dosage forms. (Immediate Release Solid Oral Dosage
839 SUPAC; Nov 1995)

840

841 **Specification:** The quality standard (i.e. tests, analytical procedures, and acceptance criteria)
842 provided in the approved application to confirm the quality of API, drug products, intermediates,
843 raw materials, reagents, components, in-process material, container closure systems, and other
844 materials used in the production of the drug substance or drug product.

845

846 **Total Impurities:** The sum of all impurities observed.

847

848 **Validation:** Establishing through documented evidence a high degree of assurance that a specific
849 process will consistently produce a product that meets its predetermined specifications and quality
850 attributes. A validated manufacturing process is one that has been proven to do what it purports or is
851 represented to do. Validation necessarily includes process qualification (the qualification of
852 materials, equipment, systems, buildings, and personnel), but it also includes the control of the
853 entire processes for repeated batches or runs.

PDA Annual Report Procedures

The PDA Annual Report is one of the most important documents prepared by staff for the membership. Proper *time* and *care* must be given to the preparation, writing, editing, review and approval of this document.

The goal is to publish and deliver to the membership the Annual Report by the end of March of the following year, i.e., March 31, 2005 for the 2004 Annual Report.

Each year, the PDA Annual Report is divided into 12 basic sections: Chair's Message, President's Message, Board of Directors, Science and Technology, Regulatory Affairs and Quality, PDA Training and Research Institute, Programs and Meetings, Membership and Chapters, Financial Report, PDA Awards, and listing of the next year's Board of Directors and PDA Staff.

Each PDA department is responsible for the content—including the accuracy and completeness—of all information in the corresponding section of the Annual Report.

Here is a summary of the procedures and expectations for the creation of this document. Each item in the following outline is explained below:

- 1. Name an individual in your department to compile information.**
- 2. Information pertaining to members must be accurate and complete.**
- 3. Rosters of volunteer members associated with your department should be available by the end of October. Revisions can be made (see below).**
- 4. Draft of Department's accomplishments should be completed by December 1.**
- 5. Complete Annual Report Verification Sign-Off Form for each version/draft of your material.**

Explanation:

1. It is advised that each department name an individual who will be in charge of compiling information for the Annual Report, including the accomplishments of the department, all rosters pertaining to their department (i.e., SAB for the Science and Technology Department, RAQC for Regulatory Affairs and Quality, Chapter Leaders for Membership and Chapters, TRI Faculty, TRI Contributors).

2. It is crucial that all information pertaining to members, i.e., committee rosters, chapter leaders, board of directors rosters, etc., be 100% accurate, complete and consistent from roster to roster. From time to time, a PDA department may contribute information or be asked to review information pertaining to a different section of the document, i.e., the President's Message and the Chair's Message.

3. Rosters should be completed and verified for completeness and accuracy by the end of October. A roster should include the names of all individuals who served on a committee, as faculty/contributor, or as a group/chapter leader during the year. Any changes to the roster in November and/or December should be forwarded to the Marketing Services department immediately via e-mail, with the subject line: "Annual Report, revision to [roster name here]". Before additions or deletions are made to the original

roster, the department head will have to verify the change (see below). Additional instructions will be supplied on how rosters should be formatted, including how to list company names.

4. Each department head will draft the initial review of their department's accomplishments for the year. The write-up should focus as much as possible on accomplishments of members, as well as the accomplishments of the PDA department. The draft should be completed by December 1 of the year for which the Annual Report is being prepared.

5. All PDA department heads will be required to sign the Annual Report Verification Sign-Off Form before the Annual Report can be prepared for final senior-staff review. The department head may be required to sign this form several times, depending on how many changes are made to their documents.

6. After all the sections of the Annual Report are submitted, verified, edited and re-verified, it will be placed into the final format. At this point, **PDA senior staff will be asked to review the document under normal PDA review/approval procedures.** Finally, the Board of Directors will be required to sign-off on the Annual Report before it is finalized and printed.

Annual Report Verification Sign-Off Form

(To be filled out by Marketing Services)

Department: _____

Department Head: _____

Document Under Review: _____

Author of Document: _____

In order for information from any department to be included in the final Annual Report, the department head must review the information and return this form. The department head must verify with their signature that they have read the document, that their department generated the document, that they or someone in their department reviewed the document for completeness and accuracy, and that there are no errors or omissions in the document.

(To be filled out by Department Head)

**I verify that I have read and reviewed the _____
for the _____ Annual Report.**

Signature: _____

Date: _____

I verify that my department generated the document.

Signature: _____

Date: _____

I verify that I and/or my staff have checked to make sure that the information in the document is complete and accurate.

Signature: _____

Date: _____

I verify that I and/or my staff have ensured that there are no errors or omissions in the information provided in the document.

Signature: _____

Date: _____