
Data Integrity and Compliance With CGMP Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Karen Takahashi 301-796-3191; (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010; or (CVM) Jonathan Bray 240-402-5623.

**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)
Center for Veterinary Medicine (CVM)**

**April 2016
Pharmaceutical Quality/Manufacturing Standards (CGMP)**

Data Integrity and Compliance With CGMP Guidance for Industry

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*Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research*

Food and Drug Administration

10001 New Hampshire Ave., Hillandale Bldg., 4th Floor

Silver Spring, MD 20993-0002

Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353

Email: druginfo@fda.hhs.gov

*<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>
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Office of Communication, Outreach and Development

Center for Biologics Evaluation and Research

Food and Drug Administration

10903 New Hampshire Ave., Bldg. 71, Room 3128

Silver Spring, MD 20993-0002

Phone: 800-835-4709 or 240-402-8010

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Policy and Regulations Staff, HFV-6

Center for Veterinary Medicine

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**Data Integrity and Compliance With CGMP
Guidance for Industry¹**

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish 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

The purpose of this guidance is to clarify the role of data integrity in current good manufacturing practice (CGMP) for drugs, as required in 21 CFR parts 210, 211, and 212. Part 210 covers Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General; part 211 covers Current Good Manufacturing Practice for Finished Pharmaceuticals; and part 212 covers Current Good Manufacturing Practice for Positron Emission Tomography Drugs. This guidance provides the Agency’s current thinking on the creation and handling of data in accordance with CGMP requirements.

FDA expects that data be reliable and accurate (see the “Background” section). CGMP regulations and guidance allow for flexible and risk-based strategies to prevent and detect data integrity issues. Firms should implement meaningful and effective strategies to manage their data integrity risks based upon their process understanding and knowledge management of technologies and business models.

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

II. BACKGROUND

In recent years, FDA has increasingly observed CGMP violations involving data integrity during CGMP inspections. This is troubling because ensuring data integrity is an important component of industry’s responsibility to ensure the safety, efficacy, and quality of drugs, and of FDA’s ability to protect the public health. These data integrity-related CGMP violations have led to

¹ This guidance has been prepared by the Office of Pharmaceutical Quality and the Office of Compliance in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research, the Center for Veterinary Medicine, and the Office of Regulatory Affairs at the Food and Drug Administration.

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42 numerous regulatory actions, including warning letters, import alerts, and consent decrees. The
43 underlying premise in §§ 210.1 and 212.2 is that CGMP sets forth minimum requirements to
44 assure that drugs meet the standards of the Federal Food, Drug, and Cosmetic Act (FD&C Act)
45 regarding safety, identity, strength, quality, and purity.² Requirements with respect to data
46 integrity in parts 211 and 212 include, among other things:

- 47
- 48 • § 211.68 (requiring that “backup data are exact and complete,” and “secure from
49 alteration, inadvertent erasures, or loss”);
 - 50 • § 212.110(b) (requiring that data be “stored to prevent deterioration or loss”);
 - 51 • §§ 211.100 and 211.160 (requiring that certain activities be “documented at the time
52 of performance” and that laboratory controls be “scientifically sound”);
 - 53 • § 211.180 (requiring that records be retained as “original records,” “true copies,” or
54 other “accurate reproductions of the original records”); and
 - 55 • §§ 211.188, 211.194, and 212.60(g) (requiring “complete information,” “complete
56 data derived from all tests,” “complete record of all data,” and “complete records of
57 all tests performed”).
- 58

59 Electronic signature and record-keeping requirements are laid out in 21 CFR part 11 and apply to
60 certain records subject to records requirements set forth in Agency regulations, including parts
61 210, 211, and 212. For more information, see guidance for industry *Part 11, Electronic Records;
62 Electronic Signatures — Scope and Application*.³ The guidance outlines FDA’s current thinking
63 regarding the narrow scope and application of part 11 pending FDA’s reexamination of part 11
64 as it applies to all FDA-regulated products.

65

III. QUESTIONS AND ANSWERS

66

1. Please clarify the following terms as they relate to CGMP records:

67

a. What is “data integrity”?

68

69

70 For the purposes of this guidance, *data integrity* refers to the completeness,
71 consistency, and accuracy of data. Complete, consistent, and accurate data should
72 be attributable, legible, contemporaneously recorded, original or a true copy, and
73 accurate (ALCOA).⁴

74

75

² FDA’s authority for CGMP comes from FD&C Act section 501(a)(2)(B), which states that a drug shall be deemed adulterated if “the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirement of the act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess.”

³ CDER updates guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

⁴ For attributable, see §§ 211.101(d), 211.122, 211.186, 211.188(b)(11), and 212.50(c)(10); for legible see §§ 211.180(e) and 212.110(b); for contemporaneously recorded (at the time of performance) see §§ 211.100(b) and 211.160(a); for original or a true copy see §§ 211.180 and 211.194(a); and for accurate see §§ 211.22(a), 211.68, 211.188, and 212.60(g).

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76 b. What is “metadata”?

77
78 Metadata is the contextual information required to understand data. A data value
79 is by itself meaningless without additional information about the data. Metadata is
80 often described as data about data. Metadata is structured information that
81 describes, explains, or otherwise makes it easier to retrieve, use, or manage data.
82 For example, the number “23” is meaningless without metadata, such as an
83 indication of the unit “mg.” Among other things, metadata for a particular piece
84 of data could include a date/time stamp for when the data were acquired, a user ID
85 of the person who conducted the test or analysis that generated the data, the
86 instrument ID used to acquire the data, audit trails, etc.

87
88 Data should be maintained throughout the record’s retention period with all
89 associated metadata required to reconstruct the CGMP activity (e.g., §§ 211.188
90 and 211.194). The relationships between data and their metadata should be
91 preserved in a secure and traceable manner.

92
93 c. What is an “audit trail”?

94
95 For purposes of this guidance, *audit trail* means a secure, computer-generated,
96 time-stamped electronic record that allows for reconstruction of the course of
97 events relating to the creation, modification, or deletion of an electronic record.
98 An audit trail is a chronology of the “who, what, when, and why” of a record. For
99 example, the audit trail for a high performance liquid chromatography (HPLC)
100 run could include the user name, date/time of the run, the integration parameters
101 used, and details of a reprocessing, if any, including change justification for the
102 reprocessing.

103
104 Electronic audit trails include those that track creation, modification, or deletion
105 of data (such as processing parameters and results) and those that track actions at
106 the record or system level (such as attempts to access the system or rename or
107 delete a file).

108
109 CGMP-compliant record-keeping practices prevent data from being lost or
110 obscured (see §§ 211.160(a), 211.194, and 212.110(b)). Electronic record-keeping
111 systems, which include audit trails, can fulfill these CGMP requirements.

112
113 d. How does FDA use the terms “static” and “dynamic” as they relate to record
114 formats?

115
116 For the purposes of this guidance, *static* is used to indicate a fixed-data document
117 such as a paper record or an electronic image, and *dynamic* means that the record
118 format allows interaction between the user and the record content. For example, a
119 dynamic chromatographic record may allow the user to change the baseline and
120 reprocess chromatographic data so that the resulting peaks may appear smaller or

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larger. It also may allow the user to modify formulas or entries in a spreadsheet used to compute test results or other information such as calculated yield.

e. *How does FDA use the term “backup” in § 211.68(b)?*

FDA uses the term *backup* in § 211.68(b) to refer to a true copy of the original data that is maintained securely throughout the records retention period (for example, § 211.180). The backup file should contain the data (which includes associated metadata) and should be in the original format or in a format compatible with the original format.

This should not be confused with backup copies that may be created during normal computer use and temporarily maintained for disaster recovery (e.g., in case of a computer crash or other interruption). Such temporary backup copies would not satisfy the requirement in § 211.68(b) to maintain a backup file of data.

f. *What are the “systems” in “computer or related systems” in § 211.68?*

The American National Standards Institute (ANSI) defines systems as people, machines, and methods organized to accomplish a set of specific functions.⁵ *Computer or related systems* can refer to computer hardware, software, peripheral devices, networks, cloud infrastructure, operators, and associated documents (e.g., user manuals and standard operating procedures).

2. When is it permissible to exclude CGMP data from decision making?

Any data created as part of a CGMP record must be evaluated by the quality unit as part of release criteria (see §§ 211.22 and 212.70) and maintained for CGMP purposes (e.g., § 211.180). Electronic data generated to fulfill CGMP requirements should include relevant metadata. To exclude data from the release criteria decision-making process, there must be a valid, documented, scientific justification for its exclusion (see the guidance for industry *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production*, and §§ 211.188, 211.192, and 212.71(b)). The requirements for record retention and review do not differ depending on the data format; paper-based and electronic data record-keeping systems are subject to the same requirements.

3. Does each workflow on our computer system need to be validated?

Yes, a workflow, such as creation of an electronic master production and control record (MPCR), is an intended use of a computer system to be checked through validation (see §§ 211.63, 211.68(b), and 211.110(a)). If you validate the computer system, but you do

⁵ American National Standard for Information Systems, *Dictionary for Information Systems*, American National Standards Institute, 1991.

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162 not validate it for its intended use, you cannot know if your workflow runs correctly.⁶ For
163 example, qualifying the Manufacturing Execution System (MES) platform, a computer
164 system, ensures that it meets specifications; however, it does not demonstrate that a given
165 MPCR generated by the MES contains the correct calculations. In this example,
166 validating the workflow ensures that the intended steps, specifications, and calculations
167 in the MPCR are accurate. This is similar to reviewing a paper MPCR and ensuring all
168 supporting procedures are in place before the MPCR is implemented in production (see
169 §§ 211.100, 211.186, and 212.50(b), and the guidance for industry *PET Drugs — Current*
170 *Good Manufacturing Practice (CGMP)*).

171
172 FDA recommends you implement appropriate controls to manage risks associated with
173 each element of the system. Controls that are appropriately designed to validate a system
174 for its intended use address software, hardware, personnel, and documentation.

4. How should access to CGMP computer systems be restricted?

175
176
177
178 You must exercise appropriate controls to assure that changes to computerized MPCRs,
179 or other records, or input of laboratory data into computerized records, can be made only
180 by authorized personnel (§ 211.68(b)). FDA recommends that you restrict the ability to
181 alter specifications, process parameters, or manufacturing or testing methods by technical
182 means where possible (for example, by limiting permissions to change settings or data).
183 FDA suggests that the system administrator role, including any rights to alter files and
184 settings, be assigned to personnel independent from those responsible for the record
185 content. To assist in controlling access, FDA recommends maintaining a list of
186 authorized individuals and their access privileges for each CGMP computer system in
187 use.

188
189 If these independent security role assignments are not practical for small operations or
190 facilities with few employees, such as PET or medical gas facilities, FDA recommends
191 alternate control strategies be implemented.⁷ For example, in the rare instance that the
192 same person is required to hold the system administrator role and to be responsible for
193 the content of the records, FDA suggests having a second person review settings and
194 content. If second-person review is not possible, the Agency recommends that the person
195 recheck settings and his or her own work.

⁶ In computer science, *validation* refers to ensuring that software meets its specifications. However, this may not meet the definition of *process validation* as found in guidance for industry *Process Validation: General Principles and Practices*: “The collection and evaluation of data ... which establishes scientific evidence that a process is capable of consistently delivering quality products.” See also ICH guidance for industry *Q7A Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients*, which defines *validation* as providing assurance that a specific process, method, or system will consistently produce a result meeting predetermined acceptance criteria. For purposes of this guidance, *validation* is being used in a manner consistent with the above guidance documents.

⁷ For further discussion of such alternate control strategies, see the guidance for industry *PET Drugs — Current Good Manufacturing Practice (CGMP)*.

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197 **5. Why is FDA concerned with the use of shared login accounts for computer**
198 **systems?**
199

200 You must exercise appropriate controls to assure that only authorized personnel make
201 changes to computerized MPCRs, or other records, or input laboratory data into
202 computerized records, and you must implement documentation controls that ensure
203 actions are attributable to a specific individual (see §§ 211.68(b), 211.188(b)(11),
204 211.194(a)(7) and (8), and 212.50(c)(10)). When login credentials are shared, a unique
205 individual cannot be identified through the login and the system would thus not conform
206 to the CGMP requirements in parts 211 and 212. FDA requires that systems controls,
207 including documentation controls, be designed to follow CGMP to assure product quality
208 (for example, §§ 211.100 and 212.50).
209

210 **6. How should blank forms be controlled?**
211

212 There must be document controls in place to assure product quality (see §§ 211.100,
213 211.160(a), 211.186, 212.20(d), and 212.60(g)). FDA recommends that, if used, blank
214 forms (including, but not limited to, worksheets, laboratory notebooks, and MPCRs) be
215 controlled by the quality unit or by another document control method. For example,
216 numbered sets of blank forms may be issued as appropriate and should be reconciled
217 upon completion of all issued forms. Incomplete or erroneous forms should be kept as
218 part of the permanent record along with written justification for their replacement (for
219 example, see §§ 211.192, 211.194, 212.50(a), and 212.70(f)(1)(vi)).
220

221 Similarly, bound paginated notebooks, stamped for official use by a document control
222 group, allow detection of unofficial notebooks as well as of any gaps in notebook pages.
223

224 **7. How often should audit trails be reviewed?**
225

226 FDA recommends that audit trails that capture changes to critical data be reviewed with
227 each record and before final approval of the record. Audit trails subject to regular review
228 should include, but are not limited to, the following: the change history of finished
229 product test results, changes to sample run sequences, changes to sample identification,
230 and changes to critical process parameters.
231

232 FDA recommends routine scheduled audit trail review based on the complexity of the
233 system and its intended use.
234

235 See audit trail definition 1.c. above for further information on audit trails.
236

237 **8. Who should review audit trails?**
238

239 Audit trails are considered part of the associated records. Personnel responsible for record
240 review under CGMP should review the audit trails that capture changes to critical data
241 associated with the record as they review the rest of the record (for example, §§
242 211.22(a), 211.101(c), 211.194(a)(8), and 212.20(d)). For example, all production and

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243 control records, which includes audit trails, must be reviewed and approved by the
244 quality unit (§ 211.192). This is similar to the expectation that cross-outs on paper be
245 assessed when reviewing data.

246

9. Can electronic copies be used as accurate reproductions of paper or electronic records?

248

249
250 Yes. Electronic copies can be used as true copies of paper or electronic records, provided
251 the copies preserve the content and meaning of the original data, which includes
252 associated metadata and the static or dynamic nature of the original records.

253

254 True copies of dynamic electronic records may be made and maintained in the format of
255 the original records or in a compatible format, provided that the content and meaning of
256 the original records are preserved and that a suitable reader and copying equipment (for
257 example, software and hardware, including media readers) are readily available (§§
258 211.180(d) and 212.110).

259

10. Is it acceptable to retain paper printouts or static records instead of original electronic records from stand-alone computerized laboratory instruments, such as an FT-IR instrument?

260

261
262
263
264 A paper printout or static record may satisfy retention requirements if it is a complete
265 copy of the original record (see §§ 211.68(b), 211.188, 211.194, and 212.60). For
266 example, pH meters and balances may create a paper printout or static image during data
267 acquisition as the original record. In this case, the paper printout or static image created
268 during acquisition, or a true copy, should be retained (§ 211.180).

269

270 However, electronic records from certain types of laboratory instruments are dynamic
271 records, and a printout or a static record does not preserve the dynamic format which is
272 part of the complete original record. For example, the spectral file created by FT-IR
273 (Fourier transform infrared spectroscopy) can be reprocessed, but a static record or
274 printout is fixed, which would not satisfy CGMP requirements to retain original records
275 or true copies (§ 211.180(d)). Also, if the full spectrum is not displayed, contaminants
276 may be excluded.

277

278 Control strategies must ensure that original laboratory records, including paper and
279 electronic records, are subject to second-person review (§ 211.194(a)(8)) to make certain
280 that all test results are appropriately reported.

281

282 For PET drugs, see the guidance for industry *PET Drugs — Current Good Manufacturing
283 Practice (CGMP)* for discussion of equipment and laboratory controls, including
284 regulatory requirements for records.

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286 **11. Can electronic signatures be used instead of handwritten signatures for**
287 **master production and control records?**
288

289 Yes, electronic signatures with the appropriate controls can be used instead of
290 handwritten signatures or initials in any CGMP required record. While § 211.186(a)
291 specifies a “full signature, handwritten,” as explained in the *Federal Register* on
292 September 29, 1978 (43 FR 45069), part of the intent of the full signature requirement is
293 to be able to clearly identify the individual responsible for signing the record. An
294 electronic signature with the appropriate controls to securely link the signature with the
295 associated record fulfills this requirement. This comports with part 11, which establishes
296 criteria for when electronic signatures are considered the legally binding equivalent of
297 handwritten signatures. Firms using electronic signatures should document the controls
298 used to ensure that they are able to identify the specific person who signed the records
299 electronically.

300
301 There is no requirement for a handwritten signature for the MPCR in the PET CGMP
302 regulations (21 CFR part 212).

303
304 **12. When does electronic data become a CGMP record?**
305

306 When generated to satisfy a CGMP requirement, all data become a CGMP record. You
307 must document, or save, the data at the time of performance to create a record in
308 compliance with CGMP requirements, including, but not limited to, §§ 211.100(b) and
309 211.160(a). FDA expects processes to be designed so that quality data required to be
310 created and maintained cannot be modified. For example, chromatograms should be sent
311 to long-term storage (archiving or a permanent record) upon run completion instead of at
312 the end of a day’s runs.

313
314 It is not acceptable to record data on pieces of paper that will be discarded after the data
315 are transcribed to a permanent laboratory notebook (see §§ 211.100(b), 211.160(a), and
316 211.180(d)). Similarly, it is not acceptable to store data electronically in temporary
317 memory, in a manner that allows for manipulation, before creating a permanent record.
318 Electronic data that are automatically saved into temporary memory do not meet CGMP
319 documentation or retention requirements.

320
321 You may employ a combination of technical and procedural controls to meet CGMP
322 documentation practices for electronic systems. For example, a computer system, such as
323 a Laboratory Information Management System (LIMS) or an Electronic Batch Record
324 (EBR) system, can be designed to automatically save after each separate entry. This
325 would be similar to recording each entry contemporaneously on a paper batch record to
326 satisfy CGMP requirements. The computer system could be combined with a procedure
327 requiring data be entered immediately when generated.

328
329 For PET drugs, see the “Laboratory Controls” section of the guidance for industry *PET*
330 *Drugs — Current Good Manufacturing Practice (CGMP)*.

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332 **13. Why has the FDA cited use of actual samples during “system suitability” or**
333 **test, prep, or equilibration runs in warning letters?**
334

335 FDA prohibits sampling and testing with the goal of achieving a specific result or to
336 overcome an unacceptable result (e.g., testing different samples until the desired passing
337 result is obtained). This practice, also referred to as *testing into compliance*, is not
338 consistent with CGMP (see the guidance for industry *Investigating Out-of-Specification*
339 *(OOS) Test Results for Pharmaceutical Production*). In some situations, use of actual
340 samples to perform system suitability testing has been used as a means of testing into
341 compliance. We would consider it a violative practice to use an actual sample in *test*,
342 *prep*, or *equilibration* runs as a means of disguising testing into compliance.
343

344 According to the United States Pharmacopeia (USP), system suitability tests should
345 include replicate injections of a standard preparation or other standard solutions to
346 determine if requirements for precision are satisfied (see USP General Chapter <621>
347 Chromatography). System suitability tests, including the identity of the preparation to be
348 injected and the rationale for its selection, should be performed according to the firm’s
349 established written procedures and the approved application or applicable compendial
350 monograph (§§ 211.160 and 212.60).
351

352 If an actual sample is to be used for system suitability testing, it should be a properly
353 characterized secondary standard, written procedures should be established and followed,
354 and the sample should be from a different batch than the sample(s) being tested (§§
355 211.160, 211.165, and 212.60). All data should be included in the record that is retained
356 and subject to review unless there is documented scientific justification for its exclusion.
357

358 For more information, see also the ICH guidance for industry *Q2(R1) Validation of*
359 *Analytical Procedures: Text and Methodology*.
360

361 **14. Is it acceptable to only save the final results from reprocessed laboratory**
362 **chromatography?**
363

364 No. Analytical methods should be capable and stable. For most lab analyses, reprocessing
365 data should not be regularly needed. If chromatography is reprocessed, written
366 procedures must be established and followed and each result retained for review (see §§
367 211.160(a), 211.160(b), 211.165(c), 211.194(a)(4), and 212.60(a)). FDA requires
368 complete data in laboratory records, which includes raw data, graphs, charts, and spectra
369 from laboratory instruments (§§ 211.194(a) and 212.60(g)(3)).
370

371 **15. Can an internal tip regarding a quality issue, such as potential data**
372 **falsification, be handled informally outside of the documented CGMP quality**
373 **system?**
374

375 No. Suspected or known falsification or alteration of records required under parts 210,
376 211, and 212 must be fully investigated under the CGMP quality system to determine the
377 effect of the event on patient safety, product quality, and data reliability; to determine the

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378 root cause; and to ensure the necessary corrective actions are taken (see §§ 211.22(a),
379 211.125(c), 211.192, 211.198, 211.204, and 212.100).

380
381 FDA invites individuals to report suspected data integrity issues that may affect the
382 safety, identity, strength, quality, or purity of drug products at DrugInfo@fda.hhs.gov.
383 “CGMP data integrity” should be included in the subject line of the email.

384
385 See also Application Integrity Policy, available at
386 <http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm>.

387
388 **16. Should personnel be trained in detecting data integrity issues as part of a**
389 **routine CGMP training program?**

390
391 Yes. Training personnel to detect data integrity issues is consistent with the personnel
392 requirements under §§ 211.25 and 212.10, which state that personnel must have the
393 education, training, and experience, or any combination thereof, to perform their assigned
394 duties.

395
396 **17. Is the FDA investigator allowed to look at my electronic records?**

397
398 Yes. All records required under CGMP are subject to FDA inspection. You must allow
399 authorized inspection, review, and copying of records, which includes copying of
400 electronic data (§§ 211.180(c) and 212.110(a) and (b)). See also section 704 of the FD&C
401 Act.

402
403 **18. How does FDA recommend data integrity problems identified during**
404 **inspections, in warning letters, or in other regulatory actions be addressed?**

405
406 FDA encourages you to demonstrate that you have effectively remedied your problems
407 by: hiring a third party auditor, determining the scope of the problem, implementing a
408 corrective action plan (globally), and removing at all levels individuals responsible for
409 problems from CGMP positions. FDA may conduct an inspection to decide whether
410 CGMP violations involving data integrity have been remedied.

411
412 These expectations mirror those developed for the Application Integrity Policy. For more
413 detailed guidance, see the “Points to Consider for Internal Reviews and Corrective Action
414 Operating Plans” public document available on the FDA Web site, accessible at
415 [http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/ucm134744.](http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/ucm134744.htm)
416 [htm](http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/ucm134744.htm).