
Guidance for Industry

Formal Dispute Resolution: Scientific and Technical Issues Related to Pharmaceutical CGMP

DRAFT GUIDANCE

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Copies of this draft guidance document are available on the Internet at <http://www.fda.gov/cder/gmp/index.htm>. For questions regarding this draft document contact Mary Jane Mathews (301) 594-2847.

**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)
Office of Regulatory Affairs (ORA)
Pharmaceutical CGMPs
August 2003**

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Additional copies of this Guidance are available from

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Internet: <http://www.fda.gov/cder/guidance/index.htm>.

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Draft Guidance For Industry¹

Formal Dispute Resolution: Scientific and Technical Issues Related to Pharmaceutical CGMP

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

I. INTRODUCTION

This document is intended to provide guidance to manufacturers of veterinary and human drugs, including human biological drug products, on how to resolve disputes of scientific and technical issues relating to current good manufacturing practice (CGMP) requirements. Disputes related to scientific and technical issues may arise during FDA inspections of pharmaceutical manufacturers to determine compliance with CGMP requirements or during the Agency's assessment of corrective actions undertaken as a result of such inspections. As these disputes may involve complex judgments and issues that are scientifically important, it is critical to have procedures in place that will encourage open, prompt discussion of disputes and lead to their resolution. This guidance describes procedures for raising such disputes to the Office of Regulatory Affairs (ORA) and center levels and for requesting review by the Dispute Resolution Panel for Scientific and Technical Issues Related to Pharmaceutical CGMP (DR Panel).

Manufacturers may seek clarification of scientific or technical issues with the inspection team at any time during an inspection. Although there are existing processes to encourage dialogue between FDA and manufacturers, the processes described in this document apply to CGMP questions raised during inspections and are intended to supplement the dispute resolution processes currently in place, including:

¹ This guidance has been prepared by the Dispute Resolution Working Group formed as part of the August 2002 FDA Initiative, Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach. The Working Group included representatives from the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), the Center for Veterinary Medicine (CVM), and the Office of Regulatory Affairs (ORA).

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- 38 • 21 CFR 10.75, Internal Agency Review of Decisions. Allows manufacturers to ask for a
39 review of Agency decisions at each successive supervisory level through the chain of
40 command, ending with the FDA Commissioner's office.
41
- 42 • CDER/CBER guidance entitled *Formal Dispute Resolution: Appeals Above the Division*
43 *Level*. Describes procedures a sponsor may use to formally appeal disputes to the office
44 or center level on scientific and procedural issues that arise during drug development,
45 new drug review, and post-marketing oversight processes. The guidance may be found
46 on CDER and CBER's Web sites².
47
- 48 • CVM draft guidance entitled *Dispute Resolution Procedures for Science-Based*
49 *Decisions on Products Regulated by the Center for Veterinary Medicine (CVM)*, May
50 2003. Describes procedures for handling requests for internal review of scientific
51 controversies relating to decisions affecting animal drugs or other products that are
52 regulated by CVM. The guidance may be found on CVM's Web site.³
53
- 54 • Investigations Operations Manual (IOM), Chapter 5, Subchapter 510, Sections 512
55 (Report of Observations) and 516 (Discussions with Management). Describes processes
56 for discussing inspectional observations with a manufacturer. The IOM is available on
57 ORA's Web site.⁴
58

59 For the purposes of this document, the term *manufacturer*⁵ includes any domestic or foreign
60 applicant or manufacturer of a human or veterinary drug, or human biological drug product
61 regulated by the Agency under the Federal Food, Drug, and Cosmetic Act (the Act) or section
62 351 of the Public Health Service Act (the PHS Act).
63

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

71 II. SCOPE OF THE GUIDANCE

72

73 The policies and procedures described in this guidance document cover all disputes on scientific
74 or technical issues related to CGMP that arise as the result of CGMP and preapproval
75 inspections (PAI) for manufacturers of veterinary and human drug products and CGMP
76 inspections for human biological drug products. For disputes that arise during prelicense and

² The CDER/CBER guidance can be found on the Internet at <http://www.fda.gov/cder/guidance/index.htm> and <http://www.fda.gov/cber/gdlns/dispute.htm>.

³ The CVM guidance can be found on the Internet at: <http://www.fda.gov/cvm/index/updates/disputegl.htm>.

⁴ The IOM can be found on the Internet at: http://www.fda.gov/ora/inspect_ref/iom/iomtc.html.

⁵ The activities of a manufacturer encompass the processes and functions described in 21 CFR 207.3(8), 21 CFR 210.3(12), and 21 CFR 600.3(t).

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77 preapproval inspections for human biological drug products or for application review issues that
78 arise during PAI inspections for human or veterinary drug products, the existing CDER/CBER
79 and CVM guidances listed in Section I of this document should continue to be used.
80

81 This guidance does not cover disputes over procedures or administrative matters that may arise
82 during the inspection process. At any time, a manufacturer may informally raise a procedural or
83 administrative matter with ORA or with the CDER, CBER or CVM Ombudsman. The
84 procedures described in this guidance do not apply to such informal dispute resolution through
85 the CDER, CBER or CVM Ombudsman.
86

III. DISPUTE RESOLUTION PROCESS

87
88
89 During inspections of manufacturers, investigators are encouraged to discuss observations
90 relating to manufacturing quality as they are observed, or on a daily basis to minimize surprise,
91 errors, and misunderstandings when a Form FDA 483 is issued. At the conclusion of an
92 inspection, investigators usually meet with the manufacturer's management to again discuss
93 observations and solicit views and additional relevant information. These processes are
94 described in detail in the Investigations Operations Manual (IOM), Sections 512 and 516, as
95 listed in Section I of this document.
96

97
98 When a scientific or technical issue arises during an inspection, we recommend that a
99 manufacturer initially attempt to reach agreement on the issue informally with the investigator.
100 A manufacturer should discuss with the investigator any observation that the manufacturer
101 believes is not justified from a scientific or technical standpoint. As appropriate, the investigator
102 can consult with FDA management or program officials, or appropriate product or technical
103 experts. If agreement on the issue is not reached with the investigator prior to issuance of the
104 Form FDA 483, a manufacturer can formally request dispute resolution after the investigator
105 issues the Form FDA 483.
106

107 Certain scientific or technical issues may be too complex or time-consuming to resolve during
108 the inspection. If resolution of a scientific or technical issue is not accomplished through
109 informal mechanisms prior to the issuance of a Form FDA 483, manufacturers can use the formal
110 two-tiered dispute resolution process described in this guidance.
111

- 112 • Tier one of the formal dispute resolution process refers to scientific or technical issues
113 raised to the ORA and center levels.
- 114 • Tier two of the formal dispute resolution process refers to scientific or technical issues
115 raised to the DR Panel.

116 These processes are described in detail in the following subsections.
117

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118 **A. Tier-One Dispute Resolution at the Office of Regulatory Affairs and Center** 119 **Levels**

120
121 Pharmaceutical manufacturers can formally dispute the scientific or technical basis for CGMP
122 inspectional observations after issuance of a Form FDA 483. In such cases, the formal dispute
123 resolution process starts in the appropriate ORA unit⁶ as listed below and may advance to the
124 applicable center.

- 125
126 • For domestic manufacturers of veterinary and human drugs, the formal dispute resolution
127 process begins in the appropriate district office, ORA.
- 128
129 • For foreign manufacturers of veterinary and human drugs, the formal dispute resolution
130 process begins in the Division of Field Investigations, ORA.
- 131
132 • For domestic or foreign manufacturers of human biological drug products inspected by
133 Team Biologics, the formal dispute resolution process begins in the Office of
134 Enforcement, ORA.

135
136 A manufacturer should seek clarification of a disputed scientific or technical issue within 10
137 business days of the completion of an inspection. FDA may refuse to address a dispute
138 resolution request not raised during this time frame.

139
140 If a manufacturer disagrees with the scientific or technical basis for an observation listed by an
141 investigator on a Form FDA 483, the following steps would be taken:

- 142
143 1. The manufacturer can file a written request for formal dispute resolution with the
144 appropriate ORA unit as listed above. The manufacturer should provide all supporting
145 documentation and arguments for review.
- 146
147 2. The appropriate ORA unit will evaluate the written request for formal dispute resolution.

148
149
150 If the ORA unit agrees with the manufacturer,

- 151
152 • The ORA unit will issue a written response to the manufacturer within 30 days of receipt
153 of the request, noting its agreement with the manufacturer and resolution of the dispute.
154 The resolution may take the form of a letter. It may also take the form of an addendum to
155 the existing Form FDA 483.
- 156
157 • All disputes resolved at the ORA level will be copied to the relevant program center for
158 information and public dissemination.

159

⁶ For the purposes of Sections III A and B in this document, the phrase *ORA unit* will refer to the district office, the Division of Field Investigations, or the Office of Enforcement, as appropriate.

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160 If the ORA unit disagrees with the manufacturer,

- 161
- 162 • The ORA unit will issue a written response to the manufacturer generally within 30 days
163 of receipt of the request. Responses that disagree with a manufacturer's position will
164 incorporate a review and decision by the relevant program center, which may require
165 additional time as described below.
 - 166
 - 167 • The written response will be copied to the relevant program center for information and
168 public dissemination after appropriate redaction, in accordance with applicable
169 requirements.
 - 170

171 If the ORA unit is unable to complete its review of the request and respond within 30 days, the
172 ORA unit will notify the manufacturer, explain the reason for the delay (which may include the
173 need for an additional 30 days for center review), and discuss the time frame for completing the
174 review.

175

176 3. If a manufacturer disagrees with the tier-one decision, the manufacturer can appeal that
177 decision to the DR Panel.

178

179 **B. Tier-Two Dispute Resolution with the DR Panel on Scientific and Technical**
180 **Issues**

181

182 The DR Panel provides a formal way for manufacturers to defend the science in their
183 manufacturing and quality control processes before a neutral panel of experts and to appeal an
184 ORA and center level decision concerning the science underlying the inspectional observation.

185

186 The DR Panel resides at the Agency level. The DR Panel considers requests for tier-two dispute
187 resolution by manufacturers and provides an opportunity for a manufacturer to present its case in
188 support of its position on a scientific or technical issue. The DR Panel's membership includes
189 representatives from each of the program centers, but will not include decision makers who have
190 addressed the disputed issue at the ORA and center level.

191

192 If a manufacturer disagrees with the tier-one decision in the formal dispute resolution process,
193 the manufacturer can file a written request for formal dispute resolution by the DR Panel. The
194 manufacturer should provide the written request for formal dispute resolution and all supporting
195 documentation and arguments to the DR Panel for review within 60 days of receipt of the tier-
196 one decision.

197

198 The DR Panel will evaluate the written request for formal dispute resolution. The DR Panel will
199 determine whether or not to consider the specific issue in the appeal. If necessary, additional
200 experts may be added to the DR Panel to facilitate evaluation of the specific issue.

201

202 If the DR Panel determines that the request is appropriate for review, it will bring the issue to the
203 next scheduled DR Panel meeting for which there is time available on the agenda.

204

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205 If the DR Panel agrees with the manufacturer on the issue,

- 206
- 207 • The executive secretary of the DR Panel will issue a written response to the manufacturer
 - 208 within 30 days of the meeting, noting its agreement with the manufacturer and resolution
 - 209 of the dispute.
 - 210
 - 211 • All disputes resolved at the DR Panel level will be copied to the relevant FDA units for
 - 212 their information and public dissemination after appropriate redaction, in accordance
 - 213 with applicable requirements.
 - 214

215 If the DR Panel disagrees with the manufacturer on the issue,

- 216
- 217 • The executive secretary of the DR Panel will issue a written response to the manufacturer
 - 218 within 30 days of the meeting, noting its decision on the issue, except as provided below.
 - 219
 - 220 • The executive secretary of the DR Panel will notify the relevant FDA units for their
 - 221 information and public dissemination after appropriate redaction, in accordance with
 - 222 applicable requirements.
 - 223

224 If the DR Panel determines that the request does not qualify for review (see Section IV), the

225 executive secretary of the DR Panel will notify the manufacturer in writing within 30 days of

226 receipt of the appeal and communicate the DR Panel's decision to the program offices.

227

228 If FDA is unable to complete its review of the request and respond within 30 days, the executive

229 secretary of the DR Panel will notify the manufacturer, explain the reasons for the delay, and

230 discuss the time frame for completing the review.

231

C. How to Request Formal Dispute Resolution

232

233

234 All Agency decisions in the formal dispute resolution process will be based on the

235 manufacturer's administrative record that was available at the time of the inspection, unless a

236 manufacturer can provide a reasonable explanation why it was unable to present relevant

237 information during the inspection. No new information should be submitted as part of a request

238 for formal dispute resolution. If a manufacturer presents new information about an issue in

239 requesting formal dispute resolution, the matter will be returned to the ORA unit for review as

240 appropriate.

241

242 The Agency may take a regulatory action under appropriate circumstances while a request for

243 formal dispute resolution is pending.

244

245 The following list of addresses can be used to request formal dispute resolution.

246

- 247 1. For a tier-one dispute resolution request from domestic manufacturers of veterinary and
- 248 human drugs, the request should be submitted to:
- 249

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- 250 Director of the district office responsible for the inspection
251 The following Internet site lists district office addresses:
252 http://www.fda.gov/ora/inspect_ref/iom/iomoradir.html.
253
- 254 2. For a tier-one dispute resolution request from foreign manufacturers of veterinary and
255 human drugs, the request should be submitted to:
256
- 257 Director, Division of Field Investigations
258 Office of Regional Operations
259 Office of Regulatory Affairs
260 Food and Drug Administration
261 Mail Code: HFC-100
262 5600 Fishers Lane, Room 13-64
263 Rockville, Maryland 20857
264
- 265 3. For a tier-one dispute resolution request from domestic or foreign manufacturers of
266 human biological drug products inspected by Team Biologics, the request should be
267 submitted to:
268
- 269 Director, Division of Compliance Management and Operations
270 Office of Enforcement
271 Office of Regulatory Affairs
272 Food and Drug Administration
273 Mail Code: HFC-210
274 5600 Fishers Lane
275 Rockville, MD 20857
276
- 277 4. For a tier-two dispute resolution request, the request should be submitted to the
278 appropriate center contact as listed below:
279
- 280 • For CDER:
281
282 Formal Dispute Resolution Project Manager (DPRM)
283 Office of Compliance
284 Center for Drug Evaluation and Research
285 Food and Drug Administration
286 Mail Code: HFD-320
287 5600 Fishers Lane
288 Rockville, MD 20857
289
 - 290 • For CVM:
291
292 Ombudsman
293 Office of the Center Director
294 Center for Veterinary Medicine

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295 Food and Drug Administration
296 Mail Code: HFV-7
297 7519 Standish Place
298 Rockville, MD 20855
299

- For CBER:

301
302 Assistant to the Director for Policy
303 Office of Compliance and Biologics Quality
304 Center for Biologics Evaluation and Research
305 Food and Drug Administration
306 Mail Code: HFM-600
307 1401 Rockville Pike, Suite 200N
308 Rockville, MD 20852
309

D. Supporting Information to be Provided by Manufacturers

310
311
312 All requests for formal dispute resolution should be in writing and include adequate information
313 to explain the nature of the dispute and to allow the Agency to act quickly and efficiently. Each
314 request should include the following:
315

1. Cover sheet that clearly identifies the submission in bold, uppercase letters:

REQUEST FOR TIER-ONE DISPUTE RESOLUTION

317
318
319
320 or

REQUEST FOR TIER-TWO DISPUTE RESOLUTION (REVIEW BY THE DISPUTE RESOLUTION PANEL FOR SCIENTIFIC AND TECHNICAL ISSUES RELATED TO PHARMACEUTICAL CGMP)

- 321
322
323
324
325
326 2. Name and address of manufacturer inspected (as listed on the Form FDA 483)
327
- 328 3. Date of inspection (as listed on the Form FDA 483)
329
- 330 4. Date the Form FDA 483 issued (from the Form FDA 483)
331
- 332 5. FEI Number, if available (from the Form FDA 483)
333
- 334 6. Names and titles of FDA employees who conducted inspection (from the Form FDA 483)
335
- 336 7. Office responsible for the inspection, e.g., district office, as listed on the Form FDA 483
337
- 338 8. Application number if the inspection was a preapproval inspection
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- 340 9. Comprehensive statement of each issue to be resolved
341
342 • Identify the observation in dispute.
343 • Clearly present the manufacturer's scientific position or rationale concerning the
344 issue under dispute with any supporting data.
345 • State the steps that have been taken to resolve the dispute, including any informal
346 dispute resolution that may have occurred before the issuance of the Form FDA 483.
347 • Identify possible solutions.
348 • State expected outcome.
349

- 350 10. Name, title, telephone and fax number, and e-mail address (as available) of manufacturer
351 contact.
352

E. FDA Response to Requests for Dispute Resolution

353
354
355 FDA will respond in writing to all requests for dispute resolution filed under the procedures
356 described in this guidance. The written response should specifically agree or disagree with the
357 outcome desired by the manufacturer, agree or disagree with parts of the proposed outcome, or
358 indicate a resolution that is different from that proposed by the manufacturer. If the Agency does
359 not agree with the manufacturer's position, the response should include reasons for the
360 disagreement.
361

362 The Agency official responsible for replying to a request for dispute resolution should make all
363 reasonable efforts to resolve the dispute and provide a written response to the manufacturer
364 according to timelines suggested above in Section III. A and B.
365
366

IV. SUITABILITY OF ISSUES FOR FORMAL DISPUTE RESOLUTION

367
368
369 Any dispute involving a scientific or technical issue related to CGMP regulations that arises
370 during an FDA inspection, as discussed above, may be suitable for the dispute resolution process
371 described in this guidance.
372

373 The following text provides examples concerning the appropriateness of several issues for the
374 dispute resolution process detailed in this guidance.
375

A. Failure to Comply With a Precise Element of CGMP Regulations

376
377
378 According to 21 CFR 211.100(a), a manufacturer producing a finished pharmaceutical product
379 must have written procedures for production and process controls, and these written procedures
380 must be designed to ensure that the drug has the identity, strength, quality, and purity it purports
381 or is represented to have.
382

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383 • Failure to have written procedures for production and process controls would be a
384 failure to comply with a precise element of the CGMP regulations and would not be
385 appropriate for the formal dispute resolution process described in this document.
386

387 • However, observations pertaining to the adequacy of the process and production
388 control design activities could be subject to scientific debate and may be appropriate
389 for dispute resolution as described in this guidance.
390

391 Another example relates to the regulatory provisions governing the testing and approval or
392 rejection of components, drug product containers, and closures (21 CFR 211.84), which require
393 appropriate sampling, testing, or examination of each lot of components, drug product
394 containers, or closures.
395

396 • Failure to conduct testing or examination of each lot would be failure to comply with
397 a precise element of the regulations and would not be appropriate for the formal
398 dispute resolution process described in this guidance.
399

400 • However, the appropriateness of a particular test or sampling scheme could involve
401 the exercise of scientific judgment. A disagreement between a manufacturer and an
402 investigator concerning the adequacy of a particular test or sampling scheme could be
403 subject to scientific debate and may be appropriate for dispute resolution as described
404 in this guidance.
405

406 A third example relates to the CGMP regulation requirements that a manufacturer thoroughly
407 investigate any unexplained discrepancy associated with its review of product production and
408 control records (21 CFR 211.192).
409

410 • Failure to investigate an unexplained discrepancy would be a failure to comply with a
411 precise element of the CGMP regulations and would not be appropriate for the formal
412 dispute resolution process described in this guidance.
413

414 • However, the extent or adequacy of the investigation could be subject to scientific
415 debate. Observations pertaining to the adequacy of an investigation into an
416 unexplained discrepancy may also be appropriate for dispute resolution as described
417 in this guidance.
418

B. Failure to Comply With a Precise Requirement Established in an Approved Application

422 If, as part of the conditions established in an approved application, a manufacturer is required to
423 conduct a particular test on a finished product and the manufacturer fails to conduct that test, this
424 failure represents a failure to comply with a precise requirement established in an approved
425 application. Any disagreement about the need for such a test should be raised in the application
426 review process, is not appropriate for the dispute resolution process described in this guidance,

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427 and should be raised using the processes described in the CDER/CBER and CVM guidances
428 listed in Section I of this document.

429

C. The Regulatory Significance of Failing to Comply With a Precise Requirement

431

432
433 The CGMP regulations require that all changes to production and process control procedures be
434 approved by the quality control unit (21 CFR 211.100(a)). If a manufacturer makes a change in
435 production and process control procedures, but does not obtain approval of those procedures by
436 the manufacturer's quality control unit, this would be a failure to comply with a precise
437 requirement of the CGMP regulations. The manufacturer may contend that the failure in this
438 particular case was not significant because it did not have an adverse effect on product quality
439 and may convey this contention to the Agency through existing informal communication
440 channels, including Form FDA 483-response correspondence.

441

442 In such a case, the significance of this observation would not be appropriate for dispute
443 resolution as described in this guidance, as the observation concerns a failure to comply with a
444 precise requirement of the regulations. The regulatory significance of an observation is
445 determined by the Agency after considering all relevant information, including the
446 manufacturer's response to the inspectional observations. The Agency encourages manufacturers
447 to provide all information relevant to the regulatory significance of an observation as part of this
448 response, but such disputes are not within the scope of this guidance on scientific and technical
449 disputes concerning the interpretation and application of CGMP requirements.

450

451 Manufacturers must have internal written production and process control procedures (21 CFR
452 211.100(a)), and, as part of these procedures, manufacturers often establish procedural *action*
453 *limits* that are tighter than release specifications. When the *action limits* are exceeded, the
454 internal written procedures may call for some type of investigation to determine if the process is
455 drifting toward a loss of control, or the procedures may call for other assessments to determine if
456 the product will meet appropriate specifications throughout its expected shelf life. If a
457 manufacturer's internal written procedures require certain actions when *action limits* are
458 exceeded, failure to follow these written production and process control procedures is a failure to
459 comply with 21 CFR 211.100(b). The manufacturer may contend that this failure is not
460 significant in that the product met all regulatory specifications when released. As discussed
461 above, this contention about significance is not appropriate for the formal dispute resolution
462 process described in this guidance.

463

D. Issues Not Raised During the Inspection

464

465
466 If, during an inspection, an investigator notes what appears to be an objectionable condition and
467 a manufacturer disagrees with that observation, the manufacturer should voice its disagreement
468 with the investigator. By doing so, the investigator has the opportunity to evaluate the
469 manufacturer's position and consult, as needed, with Agency experts. In some cases, the Agency
470 will not accept a request for dispute resolution concerning a disagreement that was not initially
471 raised by the manufacturer during the inspection. Unless the manufacturer shows it was unable

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472 to raise its disagreement during the inspection, the Agency believes that accepting such a request
473 would discourage open discussion of disagreements between investigators and manufacturers
474 and would hinder the Agency's ability to quickly and informally resolve disputes in an efficient
475 manner.

476

477

V. COMMUNICATION OF DISPUTE RESOLUTION DECISIONS

479

480 Unless the decisions made in the dispute resolution process involve information that would
481 otherwise be withheld under FDA's regulations and the applicable statutes, FDA believes that
482 decisions reached during the dispute resolution process should be made publicly available on the
483 FDA Web site after appropriate redaction, in accordance with applicable requirements.

484 Information gained from these decisions should promote consistent application and interpretation
485 of drug quality-related regulations. These decisions will be publicly available consistent with
486 FDA's good guidance practices, FDA's disclosure regulations (21 CFR Part 20), and applicable
487 statutes.