

1 **JOINT POSITION PAPER FROM EXCIPIENT MANUFACTURERS,**
2 **DRUG PRODUCT MANUFACTURERS AND USP ON**
3 **PHARMACEUTICAL EXCIPIENT**
4 **TESTING AND CONTROL STRATEGIES;**
5 **BASED ON A**
6 **PQRI SURVEY AND WORKSHOP**

7
8 Authors: Brian Carlin, Dale Carter, Gregory Larner, Kevin Moore, Barry Rothman, David
9 Schoneker, Catherine Sheehan, Rajendra Uppoor, Phyllis Walsh*, and Robert Wiens* (members
10 of the PQRI Excipient Working Group, *co-chairs)

11
12 The PQRI¹ Workshop on Excipient Testing and Control Strategies was held October 11-12, 2006
13 in Bethesda, MD. The workshop was designed to provide industry, FDA² and USP³ an
14 opportunity to interact on topics related to the testing and release of pharmaceutical excipients.
15 The results of a recently conducted PQRI industry-wide survey⁴ on the control of pharmaceutical
16 excipients were discussed in detail. Round table discussions on the impact of FDA regulations⁵,
17 guidances⁶, and the Federal Food, Drug and Cosmetic Act (FD&C Act)⁷ on excipient control
18 strategies were held and stakeholder concerns identified. Ideas were discussed for potential
19 changes in compendia, guidances and regulations to mitigate or remove redundant, duplicative,
20 or unnecessary testing on excipient batches that does not add value. Topics covered in this article
21 apply to pharmaceutical excipients that have compendial monographs in United States
22 Pharmacopoeia/National Formulary (*USP-NF*), European Pharmacopoeia (Ph.Eur.) or Japanese
23 Pharmacopoeia (JP).

24
25 Commonly used ways to control and communicate the quality attributes of excipients
26 manufactured using a continuous flow process were discussed in a round table format. Some
27 current practices for “skip” testing of excipients were examined. Ways to improve
28 pharmaceutical product quality by characterization and control of physical and chemical
29 properties of critical excipients were explored. Advantages of using independent third party
30 audits to effectively assess and ensure quality of excipients were described. The issue of
31 excipient manufacturers producing pharmaceutical grade excipients that are not tested according
32 to *USP—NF* was discussed. The workshop assessed the status of compendial harmonization and
33 its expected reduction of overall testing requirements.
34

¹ PQRI, Product Quality Research Institute, www.pqri.org

² FDA, U.S. Food and Drug Administration, <http://www.fda.gov/default.htm>

³ USP, United States Pharmacopeia, www.usp.org

⁴ PQRI Survey of Pharmaceutical Excipient Testing and Control Strategies Used by Excipient Manufacturers, Excipient Distributors, and Drug-Product Manufacturers, *Pharmaceutical Technology* Sep 2, 2006, Gregory Larner, David R. Schoneker, Catherine Sheehan, Rajendra Uppoor, Phyllis Walsh, Robert Wiens.

⁵ 21 CFR Regulations, <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm> (then, type Part and Section # in search, e.g. 211.84).

⁶ Guidance for Industry: PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance, <http://www.fda.gov/cder/guidance/6419fn1.htm>.

⁷ Federal FD&C Act, <http://www.fda.gov/opacom/laws/fdcact/fdctoc.htm>.

35 Each of the attendees had an opportunity to participate in all of the below mentioned five
36 discussion topics in a round table format. The workshop concluded with presentation of
37 summaries of round-table discussions on each topic to the entire assembly. Each presentation
38 was followed by a question and answer session. This paper will present the highlights and
39 recommended action items for each of the five topics.

40 **(1) “Continuous Flow Manufacturing” and “Skip Lot Testing”**
41 **Used for Excipients in the Context of 21 CFR Part 211.84**
42 **Regulations.**

43
44 The workshop topic description was:

45
46 The definition of “Continuous Process” as currently used by excipient manufacturers
47 does not clearly define a lot. This workshop will arrive at a commonly agreed definition
48 of a "lot" or "batch" in a continuous flow process, and a commonly agreed way to control
49 quality of excipients manufactured using a continuous flow process.

50
51 Skip lot testing is not currently used effectively and efficiently by stakeholders, and this
52 workshop will help identify and discuss best practices for use of "skip lot" testing.

53
54 Survey results noted that less than 20% of drug product manufacturers accept material based on
55 excipient manufacturer’s process controls and in-process tests not mentioned on Certificate of
56 Analysis (CoA), but providing assurance of *USP-NF* requirements. This is an area where
57 opportunities exist for excipient manufacturers and drug product manufacturers to research and
58 subsequently utilize information and knowledge that lies in the “manufacturing process-controls”
59 and “in-process test results” domain of an excipient manufacturer. Assessment of such
60 information could also confirm or otherwise indicate certain physicochemical quality aspects of
61 an excipient batch, or qualities of an excipient produced under continuous manufacturing
62 conditions.

63
64 **Definition of a “Batch” and “Lot” for Excipients Produced by Continuous Manufacturing**

65
66 It was recognized that the definitions for a “Batch” [21 CFR 210.3(b)(2)] or a “Lot” [21 CFR
67 210.3(b)(10)] applicable to manufacturing of drug products can be applied in principle to the
68 manufacturing of excipients. According to the Current Good Manufacturing Practice (cGMP)
69 regulations for finished pharmaceuticals, a “Batch” means a specific quantity of a drug or other
70 material that is intended to have uniform character and quality, within specified limits, and is
71 produced according to a single manufacturing order during the same cycle of manufacture [21
72 CFR 210.3(b)(2)]. Furthermore, a “Lot” means a batch, or a specific identified portion of a
73 batch, having uniform character and quality within specified limits; or, in the case of a drug
74 product produced by continuous process, it is a specific identified amount produced in a unit of
75 time or quantity in a manner that assures its having uniform character and quality within
76 specified limits [21 CFR 210.3(b)(10)].

77

78 Workshop participants determined that continuous flow processes can be compliant with the
79 cGMP definitions of batches and lots. It was felt that for continuous flow processes used to
80 manufacture excipients, a batch or lot can be defined by an agreement between the excipient
81 supplier or excipient manufacturer and drug product manufacturer.

82

83 **Testing of Excipient Batches**

84

85 The cGMP regulations⁸ for finished pharmaceuticals 21 CFR 211.84(d)(1) and 21 CFR
86 211.84(d)(2) require that prior to using an excipient in the manufacture of a drug product, the
87 drug product manufacturer (i) must perform at least one test to verify the excipient's identity, and
88 (ii) must demonstrate that the excipient conforms to appropriate written specifications for purity,
89 strength and quality. The cGMP regulations also specify that in lieu of such testing by the drug
90 product manufacturer for purity, strength and quality, a report of analysis may be accepted from
91 the supplier of a component (i.e., excipient), provided that at least one specific identity test is
92 conducted on such component by the drug product manufacturer, and provided that the
93 manufacturer establishes the reliability of the supplier's analyses through appropriate validation
94 of the supplier's test results at appropriate intervals.”

95

96 The cGMP regulations for component identity testing 21 CFR 211.84(d)(1) is intended to assure
97 that the component is what it purports to be on the container labeling. The cGMP regulations in
98 21 CFR 211.84(d)(2) are intended to provide sufficient flexibility to minimize, reduce or avoid
99 duplicative or repetitive testing of excipient attribute(s) when the drug product manufacturer
100 establishes the reliability of the excipient supplier's (or excipient manufacturer's) analyses.

101

102 Current industry practice for excipient manufacturers is to use in-process testing and
103 manufacturing process controls to assure batch uniformity. Such practices also are intended to
104 assure compendial compliance, and as such, not all compendial tests are routinely performed by
105 the excipient manufacturer. The CoA received by the drug product manufacturer for an
106 excipient batch may not report compendial test result(s), but will state that “if tested will meet
107 pharmacopeial requirements”. When such a statement is based on process controls, the survey
108 reported that the current practice is for the drug product manufacturer to perform the compendial
109 test(s), as required in 21 CFR 211.84(d)(1).

110

111 There are numerous scenarios where compendial tests are performed on a bulk excipient after all
112 manufacturing processes are complete, but prior to final package filling. Where an in-process or
113 bulk excipient test result is traceable to the finished excipient material, such a test result can be
114 reported on the CoA.

115

116 The determination of “critical” or “non-critical” attribute(s) of an excipient should be determined
117 by the drug product manufacturer, depending on the excipient's use in a drug product with
118 respect to its dose, dosage form, route of administration and manufacturing process(es). When a
119 drug product manufacturer wants certain tests performed on its supply of an excipient, the
120 manufacturer may need to set up a contract with the excipient manufacturer, or supplier. In any
121 case, as stated above, the CoA generated for each batch of excipient should indicate the
122 compendial (or otherwise specified) tests performed, as well as those tests not performed.

⁸ Appendix – Definitions and Regulations

123
124
125
126
127
128
129
130
131
132
133
134
135
136
137
138
139
140
141
142
143
144
145
146
147
148
149
150
151
152
153
154
155
156
157
158
159
160
161
162
163
164
165
166

Sampling for Tests by a Drug Product Manufacturer

Common sampling plans were discussed, and the assessment was that the practice of collecting $\sqrt{n + 1}$ number of samples for a shipment of excipient batch received is justifiable, where ‘n’ is the number of containers received for an excipient lot. When compositing is appropriate, $\sqrt{n + 1}$ can be a valid sampling plan.

An identity test is performed on excipient materials to determine if the material is what it purports to be and to detect any mix-up or presence of foreign material prior to use of the excipient. Current practice in many companies is to perform the identity test on a composite sample. In contrast, workshop attendees recommended that the material sampled from each individual container not be composited prior to identity testing. In other words, the samples should be tested individually for identity. This practice increases the chance of detecting incorrect or foreign material, if any present. In some situations, there can be a need for a modified approach, such as when excipients are shipped in bags on pallets, which results in a large number of bags per lot. A modified approach for sampling can be acceptable if the drug product manufacturer has procedures in place to conduct a thorough inspection of the packaging and labeling, including auditing of excipient manufactures facilities and procedures. Since each lot must at least be tested for identification, “skip lot” testing should not be used by the drug product manufacturer for the “identity test”.

Workshop attendees from many drug product manufacturers stated that they are using “skip test” procedures, based on CoA qualification and/or vendor qualification. This means that in lieu of testing samples of each lot to show that the excipient material meets its specifications, the drug product manufacturer relies on a CoA from its suppliers of excipient materials (which the drug product manufacturer has validated for reliability) to assure that each lot meets its specifications. In effect, no test is actually being skipped, because the testing to show that each lot meets all of its specifications is being performed either by the excipient or drug product manufacturer. Participants did not find any practice that needs to be changed or modified.

FDA’s Guidance for Industry, Testing of Glycerin for Diethylene Glycol

As a specific exception to the above discussion, on May 2, 2007 FDA issued a “Guidance for Industry: Testing of Glycerin for Diethylene Glycol”⁹ in which the FDA recommends that drug product manufacturers perform a specific identity test that includes a limit test for Diethylene Glycol on all containers of all lots of glycerin before glycerin is used in the manufacture or preparation of drug products. This guidance was issued due to past incidences of diethylene glycol contamination in glycerin.

Excipient Vendor Qualification, and Periodic or Skip Testing of Excipients

From the excipient survey answers on vendor qualification, 91% of drug product manufacturers stated that their vendor qualification includes Certificate of Analysis (CoA) qualification.

⁹ Testing of Glycerin for Diethylene Glycol,) issued 5/2/2007. <http://www.fda.gov/cder/guidance/7654fnl.htm>.

167 IPEC¹⁰ recommends vendor qualification as part of the CoA qualification. Vendor qualification
168 begins with receipt of a completed questionnaire¹¹, and generally followed by an on-site
169 assessment of the excipient manufacturer by a trained auditor¹². For 78% of survey respondents
170 such qualification of CoA means a reduced frequency of complete monograph testing for their
171 excipients. The reduced testing programs for 89% of drug product manufacturers included at
172 least five of their excipients. All five distributor respondents stated that a reduced testing
173 program is applicable to some, most, or all of the products they distribute. This data suggest that
174 many drug product manufacturers and excipient distributors do not perform all monograph tests
175 on their excipients after qualifying their vendors. Every 3rd lot of the excipient a drug product
176 manufacturer receives is fully tested by 3% of them, every 5th lot by 7%, and every 10th lot by
177 29%, and the remaining 61% test their excipients according to “other” frequency. The workshop
178 participants explored practices for skipping tests.

179
180 Workshop participants were confused by the terms “skip lot” and “skip test”. For this paper,
181 “skip test” or “skip testing” is the performance of specified tests at release on pre-selected
182 batches and/or at predetermined intervals, rather than on a batch-by-batch basis, with the
183 understanding that those batches not being tested still meet all acceptance criteria established for
184 that product. The use of “skip test” strategies should be identified on the Certificate of Analysis.

185
186 The ICH guidance Q6A¹³ and WHO¹⁴ each have definitions for “Periodic or Skip Testing” and
187 “Skip Lot (periodic) Testing. They are applicable to New Drug Substances and New Drug
188 Products. The ICH and WHO definitions have the same approach, yet use variations of the same
189 terms. ICH guidance Q6A states “Periodic or Skip Testing” is “the performance of specified
190 tests at release on pre-selected batches and/or at predetermined intervals, rather than on a batch-
191 by-batch basis, with the understanding that those batches not being tested still meet all
192 acceptance criteria established for that product. This represents a less than full schedule of
193 testing and should therefore be justified and presented to and approved by the regulatory
194 authority prior to implementation”. In like manner, WHO states “Skip Lot (periodic) Testing” is
195 “the performance of specified tests at release on pre-selected batches and/or at predetermined
196 intervals, rather than on a batch-to-batch basis, with the understanding that those batches not
197 tested must still meet all the acceptance criteria established for that product”. This represents a
198 less than full schedule of testing and should therefore be justified, presented to, and approved by,
199 the regulatory authority before implementation. When tested, any failure of a batch to meet the
200 acceptance criteria established for the periodic (skip lot) test should be handled by proper
201 notification of the appropriate regulatory authority(ies). If the data demonstrate a need to restore
202 routine testing, then batch-by-batch release testing should be reinstated.

203
204 The issue for each excipient batch is nonetheless to demonstrate that it conforms to all of its
205 specifications. This can be accomplished utilizing in-process testing and appropriate in-process
206 controls, and/or finished product testing.

¹⁰ International Pharmaceutical Excipients Council, <http://www.ipeec.org/>

¹¹ For example, the Excipient Information Program (EIP), IPEC-Americas.

¹² International Pharmaceutical Excipients Auditing Inc. (IPEA) <http://www.ipeainc.com>

¹³ ICH Q6A, section 2.1, <http://www.ich.org/cache/compo/276-254-1.html>

¹⁴ Good Trade and Distribution Practices for Pharmaceutical Starting Materials, World Health Organization, WHO Technical Report Series, No. 917, 2003

207
208 The workshop participants found that confusion exists because most excipient manufacturers do
209 not conduct all compendial tests since their controls give assurance that a compendial quality
210 material is produced. It was asserted that if an excipient manufacturer does not provide the result
211 for a specification test, it must be clearly indicated on the CoA, and the drug product
212 manufacturer will need to perform that test (21 CFR 211.84).

213
214 The confusion exists because in today's environment of Process Analytical Technology (PAT)
215 the question raised is do all tests really need to be run if excipient manufacturers have the
216 systems under control? This topic was felt important enough to have further discussion with
217 FDA.

218
219 **FDA Comments on Skip Testing, and Type 4 Drug Master Files for Excipients**

220
221 The workshop attendees discussed that opportunities exist for "skip testing" of excipient batches
222 by excipient manufacturers. Several conference participants suggested that the justification for
223 performing "skip testing" may be submitted to regulatory authorities (e.g., US FDA) in Type 4
224 Drug Master File (for an excipient), as allowed by 21 CFR 314.420(a)(4).

225
226 In post workshop discussions FDA representatives stated that normally, DMFs should not be
227 submitted to the Agency for standard compendial excipients unless the material is going to be
228 used in new and different ways where there may be a need for additional safety or technical data
229 on the excipient. Normally, the excipient control strategy and test justification should be
230 provided to the drug product manufacturer. The justification can then be assessed by FDA
231 during cGMP inspections of the drug product manufacturer or the excipient manufacturer.

232
233 In a post-workshop meeting, FDA representatives stated that it considers the practice of skip-
234 testing not to be compliant with cGMPs because for those lots that are not sampled and tested,
235 there is a lack of assurance that the finished excipient material will meet all of its specifications.
236 FDA believes that if an attribute for a finished raw material has required criteria, there must be
237 some measurement or test of the material in each lot to assure that the criteria are met. This may
238 be a measurement from a surrogate test, from in-process control data, or from testing or
239 measurement of the finished material in each lot. Conversely, FDA representatives believe that
240 an approach, which allows for skip testing based on a satisfactory product quality history alone is
241 not acceptable from a cGMP standpoint because such an approach does not adequately verify
242 that each lot meets all of its specifications.

243
244 FDA representatives stated that not all testing or measurements conducted to verify that a
245 finished lot of excipient material complies with its required properties must be performed on
246 samples taken from the finished lot. The representatives do not believe that testing or
247 measurement of in-process materials to verify product quality constitutes skip-testing. To assure
248 that a lot of excipient material complies with its required properties, it is acceptable to rely on
249 tests or measurements conducted on samples of material taken at an in-process stage of
250 production, provided that the in-process material will not be affected by subsequent processing
251 or holding with respect to the attributes being verified. There should be justification that test

252 results or measurements, or product performance characteristics, do not change from the in-
253 process stage to finished product.

254
255 An appropriate determination to assure that each lot conforms to appropriate specifications could
256 involve some combination of the following approaches:

- 257
- 258 • End product testing
 - 259 • In-process testing
 - 260 • Continuous monitoring of an attribute with statistical process controls
 - 261 • Documented rationale that based on the method of manufacture, the test attribute cannot
262 be present and therefore the test is not applicable, e.g., residual solvents
- 263

264 Using end product testing alone requires testing each lot of excipient material for conformance to
265 all specifications. In-process testing might involve the use of an on-line test to determine whether
266 a product attribute meets an appropriate acceptance criterion, provided that the attribute does not
267 change during the subsequent processing steps until the finished excipient is produced.

268 Continuous process monitoring with statistical process controls involves comprehensive testing
269 of an attribute using on-line monitoring and corresponding process and/or product adjustments to
270 prevent lot-to-lot variation in the product. Depending on the product and specification, any of
271 the above approaches might be appropriate for conducting a determination to ensure that each
272 batch of the product conforms to the specification.

273
274 The term “skip testing” does not actually characterize how FDA perceives testing practices in the
275 excipient industry and FDA recommends that this term not be used. The term “skip testing”
276 implies that certain required testing is not being done. Rather than “skip testing,” FDA
277 representatives recommend that the excipient industry emphasize the development and use of
278 sound sampling and testing plans for process parameters and product quality attributes. The
279 sampling plans should provide for appropriate frequency of material sampling and testing,
280 accounting for the risks identified and assurance of quality to address them, including process
281 control imperatives and intended use of the material.

282
283 The representatives stated for clarity, FDA prefers the term “measurement” instead of “test” as it
284 relates to product quality, because “measurement” conveys the correct idea of analytical testing
285 of material quality using either non-destructive in-line or on-line analytical techniques as well as
286 off-line destructive analysis commonly employed today. This approach gives excipient
287 manufacturers more latitude to use various options to verify a given product attribute.

288 289 **PAT for Excipient Manufacturing**

290
291 PAT utilizes appropriate design, analysis and control of manufacturing processes, including in-
292 process testing and controls to ensure that the finished drug product is manufactured under
293 appropriate controls. A benefit of utilizing PAT is that finished product testing can be
294 minimized by a drug product manufacturer on their final dosage forms. Therefore, the question
295 was raised, “Why can’t these same concepts be applied to excipient testing when the excipient
296 manufacturer applies similar control strategies?” Additional guidance or clarification is needed
297 from the regulatory agency(ies) on these topics.

298
299 The ICH Q6A applies to drug products, and an official clarification by FDA with a specific
300 guidance for excipients is needed. Alternatively, an industry group such as IPEC-Americas¹⁰
301 may wish to present industry guidance suitable for self-regulation. Documents in this area are
302 currently being developed by IPEC-Americas.

303 **(2) How Characterization of Excipient Physical and Chemical** 304 **Properties Helps Build Quality Into the Drug Product.**

305
306 This topic was described to the participants as:

307
308 Following the spirit of FDA's 21st Century Pharmaceutical cGMP¹⁵ and Quality by
309 Design (QbD)⁶ initiatives, the workshop will explore ways to improve product quality by
310 characterization and control of physical and chemical properties of critical excipients in a
311 given product.^{16, 17}

312
313 For the excipient survey question, about 74% of drug product manufacturers answered few or
314 none for testing excipient suitability using experimental scale (laboratory scale) drug product
315 batches or pilot scale manufacturing batches. This fact is not encouraging. Even though the
316 excipient is of compendial quality, not testing the suitability of an excipient(s) procured from
317 new vendors through laboratory or pilot scale experiments may be contributing to difficulties
318 currently encountered by drug product manufacturers during production batch scale-up
319 operations, or when an excipient is procured from different vendor(s).

320
321 Survey responses also stated, for *USP-NF* excipients, 88% of excipient manufacturers, 75% of
322 distributors, and 68% drug product manufacturers perform additional functionality or
323 processability testing that is not part of any compendial monograph (*USP-NF*, Ph.Eur., JP).
324 About three-fourths (76%) of drug product manufacturer respondents perform such tests to
325 determine excipient suitability for their intended use.

326
327 FDA's Quality by Design (QbD) and cGMPs for the 21st Century initiatives⁷ and their
328 anticipated impact on improving pharmaceutical product quality were discussed at the workshop.
329 Workshop participants recognized the value in understanding the physicochemical properties of
330 excipients that impart their functionality in the drug product, as well as their contribution to the
331 successful manufacturing of the product. It was noted that there needs to be early interaction
332 between the drug product manufacturer, and FDA for QbD-based applications to be successful.

334 **Functionality Related Characteristics**

335
336 Workshop participants noted that IPEC and USP plan to question the need for Ph.Eur. to include
337 the tests for Functionality Related Characteristics (FRCs) in monographs whether non-mandatory
338 or not. Listing non-mandatory FRCs in the monograph may provide misleading guidance and

¹⁵ http://www.fda.gov/cder/gmp/gmp2004/GMP_finalreport2004.htm#_Toc84065754

¹⁶ Excipient Functionality, R. Christian Moreton, p. 98 Pharmaceutical Technology May 2004.

¹⁷ Debating Excipient Functionality, Maribel Rios, Pharmaceutical Technology, Sep 2006, p. 50.

339 could result in drug product manufacturers not performing the studies they should to identify the
340 FRCs that matter most in connection with their use of an excipient. It may also increase the
341 possibility of non-value added testing in the supply chain. Recently PHARMEUROPA published
342 a proposed General Chapter 5.15. Functionality- Related Characteristics of Excipients which
343 explains the use of FRC in Ph. Eur.¹⁸ and how tests may be included in monographs. Workshop
344 participants agreed that a general information chapter approach is preferred which does not
345 include the listing of FRCs in monographs.

346
347 The *USP–NF* informational chapter <1059> “Excipient Performance” provides an overview of
348 the key functional categories of excipients identified in *USP–NF* along with tests that relate to
349 excipient performance. Careful consideration of the function of the excipient in the dosage form
350 and the critical attributes that relate to excipient performance will determine the need for the
351 additional tests on the excipient. The draft of <1059> “Excipient Performance” is projected for
352 publication as a Stimuli Article in Pharmacopeial Forum September –October 2007 (PF 33. 5).
353 USP’s goal is to have the draft available for discussion and feedback. USP emphasizes a
354 distinction in the <1059> information chapter tests (focus on performance testing) and those in a
355 monograph (focus on identity, strength, purity, quality). The following text from the most
356 current draft of <1059> includes such a statement.

357
358 "This Informational chapter provides an overview of the key functional categories of
359 excipients identified in *USP–NF* along with tests that may relate to excipient
360 performance. This chapter focuses primarily on those tests that are not included as
361 required tests in compendial monographs (e.g., strength, purity, identity). Careful
362 consideration of excipient function, manufacturing process, and dosage form
363 performance will allow for the selection of appropriate tests to assure that critical
364 excipient attributes relating to performance are adequately monitored and controlled."

365
366 IPEC foresees a need to continue developing our knowledge and understanding of materials and
367 processes, and how they interact to produce medicines that consistently meet the public’s
368 expectations.¹⁹ The industry should continue to work with compendia to establish a harmonized
369 approach for incorporating physical and chemical tests and analytical procedures in the General
370 Chapters of the pharmacopeias. IPEC does not support the inclusion of these tests into
371 monographs unless they may be needed to fulfill an identification requirement, e.g., test for
372 viscosity of a polymer. IPEC believes that the selection of appropriate performance related tests
373 be done by appropriate scientific investigation of the excipients used in a specific formulation in
374 a specific process using specific equipment.

375
376 Control strategies concerning excipient functionality and/or performance related tests should be
377 based on excipient manufacturer’s process capabilities and be negotiated between the excipient
378 user and excipient maker. The test parameters and control strategies which are mutually agreed
379 to should be included in contracts between the maker and user. The workshop participants
380 generally agreed with this approach.

¹⁸ PHARMEUROPA, July 2006, volume 18.3, proposed General Chapter 5.15 Functionality- Related Characteristics of Excipients.

¹⁹ Moreton C., *Excipients Performance 2006, A Technology Primer*, Supplement to Pharmaceutical Technology, p. s4, 2006.

381
382 IPEC is also supporting the development of educational programs in formulation science. Only
383 through education the industry will have the formulation scientists required by the QbD approach
384 for pharmaceuticals.

385
386 **Significant Change in Excipient Properties**

387
388 Communication to excipient users about a significant change in excipient physical and chemical
389 property(ies) should occur in a timely manner, even when the excipient would otherwise
390 continue to meet all of its compendial specifications. IPEC has defined significant change as
391 “any change by the manufacturer of an excipient that alters an excipient physical or chemical
392 property outside the limits of normal variability, or that is likely to alter the excipient
393 performance in the dosage form.” Such changes may necessitate notifying the local regulatory
394 authority if required (as in Europe). Regardless of whether there is a regulatory requirement, the
395 excipient manufacturer has an obligation to notify its customers of a significant change so that
396 the customer can evaluate the impact of the change on the customer's products. Examples of
397 significant change would include differences in the methoxylated content of
398 hydroxypropylcellulose, particle size distribution profile, change in polymorph or crystalline
399 properties, etc. The issue of change control should be part of the quality agreement between an
400 excipient user and the supplier.

401
402 Within a company, the drug product manufacturer should ensure strong oversight of supply chain
403 management decisions by R&D and other QA/technical groups. There needs to be improved
404 communication between supply chain management and technical functions, and improved
405 communication between excipient user and excipient supplier. In particular, it is very important
406 to define and evaluate significant changes to the excipient. Changes to site, scale, equipment,
407 process, packaging and labeling, and specification are considered in the IPEC-Americas
408 Significant Change Guide for Bulk Pharmaceutical Excipients.²⁰ In order to assess, evaluate, and
409 agree upon such details, audits of excipient suppliers should be a team effort by members such as
410 cGMP compliance auditors and technical personnel.

411
412 Education programs should be developed with a focus on formulation science/QbD
413 collaboratively between academia and industry.

414
415 The closing session of the workshop also identified the “need to define Significant Change in
416 Quality agreements” as a key issue.

417 **(3) Highlight Advantages of Increased Use of Third Party**
418 **Audits.**

419
420 This topic was described to the participants as:
421

²⁰ The IPEC-Americas Significant Change Guide for Bulk Pharmaceutical Excipients (First Revision, January 2005), IPEC-Americas®, 2005.

422 Third party audits of excipient manufacturers, especially outside the US, are critical to a
423 control strategy for the global excipient supply chain. The use of independent third party
424 audits may provide a cost effective way to accomplish control and ensure quality of
425 excipients, especially for smaller pharmaceutical manufacturers. The concepts and
426 advantages of independent third party audits will be described.

427
428 On-site visit by a drug product manufacturer's company auditor is the most common practice in
429 auditing an excipient manufacturer. The survey results indicated that 87% of drug product
430 manufacturers have performed auditing of their excipient manufacturers for some to all of their
431 excipients. Most drug product manufacturers do not audit every one of their excipient
432 manufacturers but instead have some type of risk prioritization process for selecting the ones to
433 audit. Only 29% of the audits were performed by third party. This is an opportunity to have third
434 party auditors provide an alternate view of the excipient supplier, and reduce the number of
435 independent audits of excipient suppliers. Of the 17 excipient manufacturers' responses, 1 stated
436 that, on average, they have on-site visit by their customers every week. Of the remaining
437 responses, 5 are visited by at least one customer once in 2 weeks; 2 manufacturers are visited by
438 their customers every 4 weeks and 8 weeks respectively, and 7 stated that they have a customer
439 at their site less often than every 8 weeks. The advantages of using independent third party audits
440 were discussed.

441
442 **Third Party Audits**

443
444 Workshop participants described the expectations of a Third Party Audit Program as including:
445 SOPs describing program operation, a Pre-Audit Questionnaire for the excipient manufacturer,
446 an established Audit Standard, clearly identified Report Content, and a policy for confidentiality
447 of audits. The Audit Standard must be based on applicable GMPs. Mr. Nicholas Buhay²¹ noted
448 that "FDA is supportive of the Joint IPEC-PQG GMP Guide for Bulk Pharmaceutical
449 Excipients." It should be noted that USP General Information Chapter <1078> Good
450 Manufacturing Practices for Bulk Pharmaceutical Excipients is based on the IPEC - PQG GMP
451 Guide for pharmaceutical excipients.

452
453 The third party should be an independent and unbiased organization and auditors. There should
454 be strong qualification and a good reputation for the organization and auditors. Auditors would
455 be trained in excipient audits and not audit the site as if it was an Active Pharmaceutical
456 Ingredient (API) and/or drug product manufacturing site. The third party audit firm should
457 provide a mock or sample audit report. Users can qualify a Third Party Audit Program by
458 comparing audit reports for the same excipient with internal audits.

459
460 The firm doing the third party audit should not consult on correction of identified issues. There
461 must be a mechanism to confirm the veracity of the findings including a review of the excipient
462 manufacturer audit report by the drug product manufacturer.

463
464 The excipient manufacturers expressed that widespread use of third party audit reports may
465 reduce the number of site audits by customers. Third Party Audits would reduce the number of

²¹ Mr. Nicholas Buhay, Deputy Director, Division of Manufacturing and Product Quality Office of Compliance, Center for Drug Evaluation and Research, FDA.

466 questionnaires from their customers. The pharmaceutical manufacturers expressed that third
467 party audits would result in more excipient manufacturers audited thoroughly and completely,
468 due to the additional time that the third party would spend on each audit. This can augment a
469 drug product manufacturer's risk management strategy for deciding on which excipient
470 manufacturer to audit, when needed.

471
472 The qualifications of the third party auditor should include training, and a general audit
473 background. Qualifications should include formal recognition such as ASQ Certified Quality
474 Auditor, or ISO 9001 Certified Lead Auditor, or other recognized Auditor Training Course.
475 Familiarity with IPEC Excipient GMPs is essential along with appropriate audit experience and
476 background. The qualifications may include experience in API audits, and an understanding of
477 the regulated environment. The auditor should be knowledgeable on differences between 21
478 CFR Part 211 and USP General Information Chapter <1078>. They can prioritize/categorize
479 audit observations, know what is important to audit, and know what findings are important. In
480 summary, the auditor must demonstrate audit competency.

481
482 The benefits of third party audits to small drug product manufacturers include that the audit has
483 more credibility than a questionnaire alone. Many small drug manufacturers do not have the
484 resources to audit many of their excipient manufacturers other than the ones they may consider
485 absolutely critical. Since they are not able to routinely audit their excipient manufacturers, they
486 currently only use questionnaires. A concern with just using a questionnaire is how do you know
487 the answers are truthful? The use of third party audits may offer a good alternative. With third
488 party audits, a small drug product manufacturer can avoid a staff of auditors, can reduce the
489 number of audits (especially outside the US), and at the same time have more confidence in their
490 excipient manufacturer. This strategy allows small drug product manufacturers to assess more
491 excipient producers more reliably. A small drug product manufacturer would use the audit to
492 help assure them that their supplier qualification program is adequate.

493
494 The workshop attendees identified International Pharmaceutical Excipients Auditing, Inc.
495 (IPEA²²) and the USP-Pharmaceutical Ingredient Verification Program²³ as examples of
496 organizations and programs that perform qualified third party audits.

497 **(4) Strategies to Increase Number of Excipients Labeled** 498 ***USP-NF***

499
500 This topic was described to the participants as:

501
502 There is an increasing danger of excipient manufacturers not producing pharmaceutical
503 grade excipients that meet *USP-NF* criteria, which creates an enormous problem for the
504 drug manufacturing industry. This concern is exacerbated by the fact that, *USP-NF* is
505 missing monographs for some commonly used excipients. The workshop will assess
506 these issues, and propose solutions to preempt the issue of reduced numbers of excipients
507 labeled *USP-NF*.

²² www.ipeainc.com

²³ <http://www.usp.org/USPVerified/pharmaceuticalIngredients/>

508
509 Approximately 40% of drug product manufacturers and 1 out of 4 distributors reported that they
510 had difficulty in finding a manufacturer of a *USP-NF* grade excipient. The survey findings
511 indicated that most of the excipient manufacturers and distributors who responded label their
512 excipients as compendial grade. However, it is noteworthy that 11% of excipient manufacturers
513 and 1 out of 5 excipient distributors are not choosing to label their products as compendial grade.
514 The reason(s) for not labeling their excipients as compendial grade could not be accurately
515 determined from the responses to this survey. The authors have experienced a growing number
516 of situations where excipient manufacturers are dropping the compendial grade label suffix, i.e.
517 USP, NF, Ph.Eur., JP, either because of the increasing cGMP expectations and/or low volumes
518 sold to the pharmaceutical market, combined with efforts required to meet pharmaceutical
519 manufacturers' expectations. The current situation was explored by the workshop participants.

520 521 **Compendia and Compliance** 522

523 Currently, the FDA Compliance Policy Guide (CPG) Section 420.400, Performance of Tests for
524 Compendial Requirements on Compendial Products states; "Compendial methods need only be
525 applied, as a batch release test, where a firm has made specific commitments to do so (as in a
526 new drug application), or where the official method is the only appropriate test. It should be
527 noted that neither the *USP-NF* nor the cGMP regulations necessarily require a firm to utilize, as
528 a batch release test, the methods and procedures stated in the official compendia. Alternate tests
529 (including in-process analyses) can therefore be used in lieu of USP tests²⁴.

530 More specifically, official drug products are required to conform to the compendial standards
531 and monograph requirements. This conformance must be assured by suitable means, including
532 adequate manufacturing process validation and control. Scientifically sound alternative test
533 methods may be acceptable for the purpose of batch release testing. However, in the event of a
534 dispute as to whether or not a compendial article meets the standard, the pharmacopeial method
535 and analytical procedures will be applied as the referee test". This applies to official substances,
536 official preparations (finished dosage forms) and excipients.

537
538 CPG section 420.400 continues "Where an official product purports to conform to the standards
539 of the *USP-NF*, the manufacturer must assure that each batch conforms to each monograph
540 requirement. This assurance must be achieved by appropriate means, including process
541 validation and controls and end product testing. However, the nature and extent of end product
542 testing which is needed will depend upon the circumstances. Factors to consider in determining
543 the need to test each batch for a given monograph requirement include: the adequacy of the
544 manufacturer's process validation, adequacy of in-process manufacturing controls, and the nature
545 of the particular product characteristic which is the subject of the specification (e.g. potency,
546 sterility, content uniformity). Therefore, in some cases it may not be necessary for a
547 manufacturer to test each batch for each monograph requirement".

548
549 In post workshop meetings, FDA representatives said that CPG section 420.400 is under
550 revision. The intent of this CPG is not to provide for a skip test approach. There must be

²⁴ USP30 General Notices; Section Tests and Assays – Procedures.

551 appropriate testing and measurement of in-process and/or finished product samples from each
552 batch to assure that the finished material complies with all compendial requirements.
553

554 **Federal Food, Drug and Cosmetic Act and 21 CFR**
555

556 During the workshop and at the closing session, it was noted that Section 501(b) of the FD&C
557 Act²⁵ applies to all articles recognized in an official compendium. Further, Section 201(g) of the
558 Act defines a drug in part as an article recognized in the official USP and NF, as well as an
559 article intended for use as a component of a drug or drug product. Consequently, *USP–NF*
560 excipients intended for the drug market must comply with *USP–NF* standards, whether or not
561 the labeling on shipments of the excipient include the *USP–NF* designation.
562

563 Also Section 501(a)(2)(B) of the FD&C Act requires that drugs (including excipients meeting
564 the definition of a drug in Section 201(g) of the Act), be manufactured in conformance with
565 current good manufacturing practice. Hence, according to the Act, all excipients intended for
566 use in the manufacture of a drug product, whether or not the excipient is listed in the official
567 *USP–NF*, must be manufactured in conformance with current good manufacturing practice.
568 However, FDA has not promulgated cGMP regulations for excipients. The cGMP regulations in
569 21 CFR Parts 210 and 211²⁶ apply to the manufacture of finished drug products, and not to the
570 manufacturing of APIs or excipients. Therefore, GMP guidance for pharmaceutical excipients
571 has been jointly published by IPEC and PQG.²⁷
572

573 **Issue of Excipient Manufacturers Removing USP or NF Designation from the Label**
574

575 During the workshop it was noted that some manufacturers of pharmaceutical excipients remove
576 the USP or NF designation from labeling to avoid having to conform to current good
577 manufacturing practice and official *USP–NF* standards. It was noted by FDA however, that
578 removing the USP or NF labeling does not obviate the requirement to meet applicable current
579 good manufacturing practice and official *USP–NF* standards.
580

581 Workshop participants highlighted several questions and answers. First, what is industry's
582 burden in supplying analytical methods validation data to regulatory agency for excipients no
583 longer labeled USP or NF? This is an important topic, and there was no real answer at the
584 conference. However, the drug product manufacturer needs to find out the reasons why the
585 excipient manufacturer is removing the USP or NF designation. Is it because they cannot meet
586 the specification? Is it due to GMP issues? For specification issues, excipient manufacturers can
587 work with the USP. For GMP issues, the drug product manufacturer must carefully assess the
588 suitability of supplier's GMPs for the intended use. If the supplier stopped designating the
589 excipient as USP or NF for GMP reasons, then the material from such a supplier should not be
590 used and a different acceptable supplier for that material should be found.
591

²⁵ See Appendix below.

²⁶ CFR Title 21-Food & Drugs Good Manufacturing Practice, Part 211.

²⁷ Joint IPEC – PQG Good Manufacturing Practice Guide For Pharmaceutical Excipients 2006. Available at <http://www.ipecamericas.org/>.

592 A second question was if the drug manufacturer references the excipient manufacturer's DMF,
593 does the drug manufacturer need to supply the analytical methods validation data? The answer
594 was that no additional analytical methods validation data need to be supplied in an abbreviated
595 new drug application or new drug application (ANDA or NDA), if FDA determines the DMF to
596 be adequate in support of an application.

597
598 After the workshop, the PQRI Excipient Working Group discussed the regulatory and
599 implementation recommendations to address these two topics. Although the regulations do not
600 directly apply, the following practices can apply.

601
602 **Analytical Methods Validation Data for Non-Compendial Analytical Procedures Used for**
603 **Testing Non-Compendial Designated Excipient**

604
605 When an excipient manufacturer or drug product manufacturer uses a non-compendial (or other
606 FDA recognized public standard) analytical procedure for testing a not novel²⁸, non-compendial
607 designated component for which official *USP-NF* monograph exists, the analytical methods
608 validation data for such test procedures should be made available for review by the regulatory
609 agency (e.g., FDA) at the site of excipient testing.

610
611 If the excipient manufacturer were to submit the alternative analytical procedure and its
612 analytical methods validation data in a Type 4 DMF²⁹, then, the drug product manufacturers can
613 reference it in their drug applications, and need not submit the same information again for
614 Agency's review.

615
616 A not-novel, or non-novel, or a new excipient can be a non-GRAS (Ref: substances Generally
617 Recognized As Safe, 21 CFR Parts 182, 184, 186³⁰) component used for the first time in a human
618 drug product, or a previously used drug product component proposed for use in higher quantity
619 per dose or per daily human exposure, or by a new route of administration, or for a longer
620 duration of human use than previously evaluated and allowed by FDA. Additional details on this
621 subject can be found in FDA's Guidance for Industry³¹.

622
623 A "non-compendial designated component" is an article for which an official NF or USP
624 monograph exists; and the article in all probability will meet *USP-NF* end-product test criteria if
625 and when tested; and an article for which the excipient (article) manufacturer chooses "not to
626 designate" on its label the USP or NF designation or suffix, even when each batch of the
627 excipient would have passed the *USP-NF* end-product test criteria by a compendial analytical
628 procedure, or by an alternate analytical procedure.

629

²⁸ Guidance for Industry: M4Q: The CTD - Quality ICH CTD, Section 2.3.P.4.6.,
<http://www.fda.gov/cder/guidance/4539Q.htm>

²⁹ Guideline For Drug Master Files; <http://www.fda.gov/cder/guidance/dmf.htm>; Also see IPEC Excipient Master
File Guideline, Available at <http://www.ipecamericas.org/>.

³⁰ substances Generally Recognized As Safe, 21 CFR Parts 182, 184, 186;
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm>

³¹ Guidance for Industry; Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients;
<http://www.fda.gov/cder/guidance/5544fnl.htm>

630 A non-compendial analytical procedure is an end-product test procedure that is not described in a
631 pharmacopeia. An alternate analytical procedure is other than a compendial analytical procedure
632 or other FDA recognized public standard³² procedure such as those published in FCC, AOAC
633 International, ASTM³³ standard procedure, etc. For a compendial analytical procedure, the
634 FDA does not expect to receive analytical methods validation data in a drug product application.
635 A reference to the official compendial procedure, or a FDA recognized public standard analytical
636 procedure would suffice. Validation data for non-compendial analytical procedures should be
637 made available for inspection at the testing site, and need not be submitted in an application.

638
639 If a drug product manufacturer tests every batch of a non-compendial designated excipient they
640 receive using compendial analytical procedures, then, it would amount to a practice of verifying
641 their excipient quality by testing. A substantive issue in that case can be whether the excipient
642 was manufactured under GMP conditions²⁷ or not.

643
644 At the workshop it was discussed that some extensively used excipients do not have monographs
645 in *USP-NF*. On the other hand, there are *USP-NF* monographs without excipient manufacturers
646 supplying USP or NF grade material.

647
648 The following excipients are used by the pharmaceutical industry which do not have current
649 monographs in *USP-NF*; Corn Syrup, Edetate Calcium (Calcium EDTA powder), Propylene
650 Glycol Stearate, Propylene glycol diacetate, and Gentisic acid ethanolamide. Diethyl Phthalate,
651 Liquid Glucose, and Lecithin do not have excipient manufacturers producing NF grade material.
652 Additional supply problems occur with particular grades, such as synthetic Glycerin. For
653 Lecithin, some grades are available, but others are not.

654
655 USP provides assistance in the form of Submission Guidelines³⁴ for an excipient monograph or
656 revision to an existing monograph to the *USP-NF*.

657
658 Workshop participants agreed that FDA providing additional guidance to excipient
659 manufacturers may alleviate some of these issues. USP has already published IPEC guidelines
660 as a general information chapter, <1078> GMPs for Bulk Pharmaceutical Excipients. These
661 guidelines also educate the drug manufacturer with regard to excipient GMP and other
662 expectations.

663

664 **(5) Reduced Testing Due to Use of Compendial** 665 **Harmonization**

666

667 This topic was described to the participants as:

668

³² 21 CFR 211.194(a)(2); <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfrcfr/CFRSearch.cfm?fr=211.194>

³³ ASTM International; www.ASTM.org

³⁴ USP Submission Guide; Chapter 3 Excipients and addenda;
<http://www.usp.org/USPNF/submitMonograph/subGuide.html>

669 By increasing the pace of global harmonization, industry stakeholders are expecting to
670 reduce testing significantly. The workshop will assess the status of harmonization and
671 will recommend how to effectively use harmonized monographs, and reduce the testing
672 burden of pharmaceutical excipients.

673
674 Over half of excipient manufacturers (59%) and of drug product manufacturers (55%) reduce
675 redundant testing by selecting the most stringent method or specification for confirming
676 compliance with more than one compendium. About 53% of excipient manufacturers and 74%
677 of drug product manufacturers stated that redundant testing could be reduced by at least 20%.
678 Only two respondents indicated redundant testing would not be reduced.

679
680 As more excipient and drug product manufacturers operate globally, the use of harmonized
681 monographs will only grow. Presently, a majority of stakeholders use the most stringent test
682 method, specification, or acceptance criteria for compliance, or may also test for the same
683 attribute using another pharmacopeial analytical procedure, resulting in redundant testing of the
684 same attribute. Drug product manufacturers would like the option of using a specification (test
685 for an attribute, analytical procedure, and acceptance criteria) for a drug substance or excipient
686 from the current edition of the British Pharmacopoeia (BP), Ph.Eur., or JP monograph as part of
687 the specifications in a drug application. This approach would aid the use of test methods where
688 the analytical procedure and acceptance criteria in the BP, Ph.Eur., or JP monograph are
689 equivalent or superior to the analytical procedure and acceptance criteria in the corresponding
690 *USP–NF* monograph. This option would be helpful for both drug substance and excipient
691 monographs.

692
693 The workshop discussed the effective use of harmonized monographs. Excipient and drug
694 product manufacturers envisioned two ways going forward – (i) harmonization (full) or (ii)
695 mutual acceptance of the other pharmacopoeias by the regulators. As stated in USP general
696 information chapter <1196> Pharmacopeial Harmonization, “A pharmacopeial general chapter
697 or other pharmacopeial document is harmonized when a pharmaceutical substance or product
698 tested by the document’s harmonized procedure yields the same results and the same
699 accept/reject decision is reached.” Further details of ongoing effort and activities by the
700 Pharmacopeial Discussion Group (PDG) and the ICH on this subject can be found in the ICH
701 Step 2 document, “Q4B Regulatory Acceptance of Analytical Procedures and/or Acceptance
702 Criteria (RAAPAC)” available at FDA’s website³⁵.

703
704 The closing questions and comments of the workshop observed that one word in the CFR 211.84
705 that causes confusion is the use of the term – “test” instead of a term such as “evaluate”. It was
706 pointed out that excipient manufacturers are not going to perform every compendial test on
707 samples of finished material if it is not necessary to perform such tests to demonstrate control of
708 their processes and adequate product quality. Also, there is no requirement for excipient
709 manufacturers to perform compendial tests on finished material as a release test. It apparently
710 was not understood that the cGMP regulations in 21 CFR Parts 210 and 211 apply to
711 manufacturers of finished dosage forms, and not to the manufacturers of excipients. As such, the
712 requirements in 21 CFR 211.84, do not apply to excipient manufacturers. Nevertheless,
713 excipient manufacturers should have appropriate control processes in place along with sufficient

³⁵ <http://www.fda.gov/cder/guidance/7386dft.htm> (also see 71 FR 45059, dated August 8, 2006)

714 testing and measurement to assure that each finished lot of excipient meets all of its quality
715 requirements.

716
717 **Use of a ICH Q4B Harmonized Compendial Procedure Published in USP– NF or its**
718 **Supplement, with a Future Implementation Date**

719
720 When a new compendial procedure or a general chapter is published in *USP– NF* or its
721 supplement with a future implementation date, an excipient manufacturer or a drug product
722 manufacturer may begin voluntarily to use such new procedure or general chapter, before the
723 published implementation date. In general, FDA has not objected to such a practice. In other
724 words, before the implementation date of a published harmonized procedure, either the current
725 official procedure, or the new harmonized procedure may be used for testing. However, after the
726 official implementation date of an ICH harmonized new procedure or a *USP-NF* General
727 Chapter (specifically, those numbered between <1> and <999>), the new procedure becomes
728 effective and enforceable by the FDA.

729
730 The issue of post approval compendial changes was also discussed at the workshop. A post-
731 approval change submission to a NDA or ANDA application should be relevant to the
732 information originally contained in the application. In general, changes in an excipient
733 specification to comply with compendial requirements would not require any notification to FDA
734 for non-application drug products. For drug products approved by the Agency through an
735 application, FDA’s “Guidance for Industry, Changes to an Approved NDA or ANDA;
736 Specifications – Use of Enforcement Discretion for Compendial Changes” published November
737 2004 recommends filing an annual report for all excipient specification changes made to comply
738 with the official compendium. FDA should revise regulations e.g. 21CFR 314.70 to clarify this
739 issue.

740 **Summary and Recommendations**

741
742 **(1) “Continuous Flow Manufacturing” and “Skip Lot Testing” Used for Excipients**

743
744 Discussions with FDA resolved several issues beginning with definitions of “batch” and “lot” as
745 applied to continuous flow manufacturing. A “Batch” means a specific quantity of a drug or
746 other material that is intended to have uniform character and quality, within specified limits. A
747 “Lot” means a batch, or a specific identified portion of a batch. The continuous flow
748 manufacturing process may have a batch or lot defined by agreement between the supplier or
749 manufacturer and customer.

750
751 The term “skip lot testing” does not correctly reflect current practice. Wherever an in-process or
752 bulk excipient test result is traceable to the final package, that test result can be reported in the
753 CoA.

754
755 A sampling plan based on $\sqrt{n} + 1$ containers sampled is appropriate for creating a composite
756 sample. Common practice is to perform the identity test on the composite sample. It was
757 suggested that identity tests should be performed on samples collected from individual containers
758 and not use a composite sample.

759
760
761
762
763
764
765
766
767
768
769
770
771
772
773
774
775
776
777
778
779
780
781
782
783
784
785
786
787
788
789
790
791
792
793
794
795
796
797
798
799
800
801
802
803

(2) Characterization of Excipient Physical and Chemical Properties to Help Build Quality into the Drug Product.

Additional functionality or processability testing beyond the compendial monograph testing is performed by a great majority of excipient manufacturers, distributors, and drug product manufacturers. This approach is consistent with FDA’s Quality by Design, and cGMPs for the 21st Century initiatives. As proposed by *USP– NF*, compendial support of functionality testing should be presented in a general chapter with references to tests appropriate to the desired function. Drug product manufacturer and excipient manufacturer should mutually agree to the correct control strategy.

Communication to excipient users about a significant change in excipient physical and chemical property(ies) should occur in a timely manner, even when the excipient would otherwise continue to meet all of its compendial specifications. The issue of change control should be part of the quality agreement between an excipient user and the supplier.

(3) Advantages of Third Party Audits.

Audits are a key part of supply chain management, and are commonly performed by the auditors of the drug product manufacturer. Audits should be based on a uniform standard such as the USP General Information Chapter <1078> which is based on the IPEC GMP Guide for Bulk Pharmaceutical Excipients. The benefit to excipient manufacturers is a reduction in site audits and questionnaires from their customers. The benefit to drug product manufacturers is a more thorough and complete audit due to the additional time spent by the third party. A small drug manufacturer would have a more credible assessment than by a questionnaire alone.

(4) Strategies to Increase Number of Excipients Labeled *USP–NF*

The FD&C Act required that official drug products and excipients that have pharmacopeial monographs must conform to compendial standards whether or not they are labeled as USP or NF. Conformance to compendial specifications may be assured by adequate manufacturing process validation, in-process controls, and through in-process tests or measurements of excipient quality.

About 40% of drug product manufacturers experience the loss of an NF label for an excipient. When a compendial excipient is not labeled USP or NF, the reason for not designating the component as USP or NF by the excipient manufacturer should be determined.

The reasons an excipient manufacturer drops the USP or NF designation include low volumes sold to the pharmaceutical industry and the perceived cost of maintaining GMP compliance. This can be overcome by quality and risk assessments such as audits to verify GMP compliance and compendial testing. It was expressed that when an excipient source does not maintain GMP compliance, the drug product manufacturer needs to obtain a new source for that material.

804 Alternative test methods may be used for batch release testing, but if there is a dispute, the
805 compendial test is applied as the standard. Use of alternative test methods like ACS, AOAC
806 International, Ph.Eur., or JP will generally require verification, but not validation. Analytical test
807 method validation data in support of alternative analytical procedures should be kept for
808 inspection at the excipient testing site. When a DMF is referenced in an NDA/ANDA, the drug
809 product manufacturer does not need to submit additional analytical test method validation data
810 unless FDA determines the DMF to be inadequate.

811
812 When an excipient monograph is not found in *USP–NF*, contact USP for resources to create the
813 monograph. The workshop found that additional FDA guidance to excipient manufacturers may
814 alleviate some of these issues. USP has published the Joint IPEC-PQG GMP Guide, and this
815 guideline may also educate the drug manufacturer regarding excipient GMP and specific ways
816 the GMPs are applied to the excipient manufacturer.

817

818 **(5) Use of Reduced Testing Due to Use of Compendial Harmonization**

819

820 Over half of excipient and drug product manufactures reduce redundant testing by selecting the
821 most stringent method or specification for confirming compliance with more than one
822 compendium. The addition of more harmonized monographs is very helpful to industry, but
823 further success depends on either full harmonization or mutual acceptance of the other
824 pharmacopoeias by regulators.

825

826 Conference participants indicated that the term “test” in 21 CFR 211.84 creates confusion in the
827 excipient industry. Post-workshop conversations with FDA remind us that 21 CFR 211.84
828 applies to drug products. Especially for continuous manufacturing processes, the excipient
829 industry should apply “tests and measurements” in the control strategies of excipients. These
830 control strategies are viewed as good examples of PAT concepts in practice. The tests and
831 online measurements can give assurance of compliance to compendial standards. Assurance of
832 compliance is demonstrated if test and measurement methods are validated, compared to
833 compendial test method results, and linked to the excipient in the final package. Such
834 documentation justifies the reporting content of the excipient CoA, and should be available at the
835 excipient manufacturing or testing site.

836

837 Where USP publishes a harmonization chapter with delayed implementation dates, FDA will not
838 enforce the new chapter until the implementation date. Either the current official procedure or
839 the new published procedure may be voluntarily used between publishing a change and the
840 implementation date.

841

842 Workshop participants stated that in general, changes in excipient specifications to comply with
843 compendial requirements would not require any notification to FDA for non-application (e.g.,
844 over-the-counter) drug products. For drug products approved by the Agency through an
845 application (e.g., NDA, ANDA, BLA), FDA’s “Guidance for Industry, Changes to an Approved
846 NDA or ANDA; Specifications – Use of Enforcement Discretion for Compendial Changes”
847 recommends filing an annual report for all excipient specification changes made to comply with
848 the official compendium.

849

850 Further discussions are scheduled at the 2007 IPEC-Americas Regulatory Affairs Conference¹⁰,
851 September 10-11, in Alexandria, VA. In particular, this paper will be the basis for the section
852 “Excipient Testing, Control and Communication: Findings of a PQRI Working Group”. The
853 stakeholders may further benefit by attending this conference.

854 **Appendix – Definitions and Regulations**

855 **Federal Food, Drug, and Cosmetic Act**

857 Chapter II – Definitions:
858

859
860 Section 201(g)(1) The term “drug” means; (A) articles recognized in the official United States
861 Pharmacopeia, official Homeopathic Pharmacopeia of the United States, or official National
862 Formulary, or any supplement to any of them; (B) articles intended for use in the diagnosis, cure,
863 mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other
864 than food) intended to affect the structure or any function of the body of man; and (D) articles
865 intended for use as a component of any articles specified in clause (A), (B), or (C).
866

867 Section 201(j) -The term “official compendium” means the official United States Pharmacopeia,
868 official Homeopathic Pharmacopeia of the United States, official National Formulary, or any
869 supplement to any of them.
870

871 Chapter V - Adulteration sections:
872

873 A drug or device shall be deemed to be adulterated -- Section 501(a)(2)(B) If it is a drug and the
874 methods used in, or the facilities or controls used for, its manufacture, processing, packing, or
875 controls used for, its manufacture, processing, packing, or holding do not conform to or are not
876 operated or administered in conformity with current good manufacturing practice to assure that
877 such drug meets the requirements of this Act as to safety and has the identity and strength, and
878 meets the quality and purity characteristics, which it purports or is represented to possess or is
879 represented to possess.
880

881 A drug or device shall be deemed adulterated -- Section 501(b) If it purports to be or is
882 represented as a drug the name of which is recognized in an official compendium, and its
883 strength differs from, or its quality or purity falls below, the standards set forth in such
884 compendium. Such determination as to strength, quality, or purity shall be made in accordance
885 with the tests or methods of assay set forth in such compendium, except that whenever tests or
886 methods of assay have not been prescribed in such compendium, or such tests or methods of
887 assay as are prescribed are, in the judgment of the Secretary, insufficient for the making of such
888 determination, the Secretary shall bring such fact to the attention of the appropriate body charged
889 with the revision of such compendium, and if such body fails within a reasonable time to
890 prescribe tests or methods of assay which, in the judgment of the Secretary, are sufficient for
891 purposes of this paragraph, then the Secretary shall promulgate regulations prescribing
892 appropriate tests or methods of assay in accordance with which such determination as to
893 strength, quality, or purity shall be made. No drug defined in an official compendium shall be
894 deemed to be adulterated under this paragraph because it differs from the standard of strength,

895 quality, or purity therefore set forth in such compendium, if its difference in strength, quality, or
896 purity from such standards is plainly stated on its label. Whenever a drug is recognized in both
897 the United States Pharmacopeia and the Homeopathic Pharmacopeia of the United States it shall
898 be subject to the requirements of the United States Pharmacopeia unless it is labeled and offered
899 for sale as a homeopathic drug, in which case it shall be subject to the provisions of the
900 Homeopathic Pharmacopeia of the United States and not to those of the United States
901 Pharmacopeia.

902
903

904 **Title 21 Code of Federal Regulations**

905
906
907
908

Parts 210 and 211 - CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED
PHARMACEUTICALS

909 211.84(d) Samples shall be examined and tested as follows:

910 (1) At least one test shall be conducted to verify the identity of each component of a drug
911 product. Specific identity tests, if they exist, shall be used.

912 (2) Each component shall be tested for conformity with all appropriate written specifications for
913 purity, strength, and quality. In lieu of such testing by the manufacturer, a report of analysis may
914 be accepted from the supplier of a component, provided that at least one specific identity test is
915 conducted on such component by the manufacturer, and provided that the manufacturer
916 establishes the reliability of the supplier's analyses through appropriate validation of the
917 supplier's test results at appropriate intervals.

918 21 CFR 211. 194 (a) (2) - A statement of each method used in the testing of the sample. The
919 statement shall indicate the location of data that establish that the methods used in the testing of
920 the sample meet proper standards of accuracy and reliability of the sample meet proper standards
921 of accuracy and reliability as applied to the product as applied to the product tested. (If the
922 method employed is in the current revision of the United States Pharmacopeia, National
923 Formulary, AOAC INTERNATIONAL, Book of Methods, or in other recognized standard
924 references, or is detailed in an approved new drug application and the referenced method is not
925 modified, a statement indicating the method and reference will suffice). The suitability of all
926 testing methods used shall be verified under actual conditions of use.

927
928
929

21 CFR 314.70 Supplements and other changes to an approved application:

930 (d) Changes to be described in an annual report (minor changes): (1) Changes in the drug
931 substance, drug product, production process, quality controls, equipment, or facilities that have a
932 minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency
933 of the drug product as these factors may relate to the safety or effectiveness of the drug product
934 must be documented by the applicant in the next annual report in accordance with 314.81(b)(2).
935 (2) These changes include, but are not limited to:

936 (i) Any change made to comply with a change to an official compendium, except a change
937 described in paragraph (c)(2)(iii) of this section, that is consistent with FDA statutory and
938 regulatory requirements.

939

940 21 CFR 314.70 (c) Changes requiring supplement submission at least 30 days prior to
941 distribution of the drug product made using the change (moderate changes).

942 (2) These changes include, but are not limited to:

943 (iii) Relaxation of an acceptance criterion or deletion of a test to comply with an official
944 compendium that is consistent with FDA statutory and regulatory requirements.

945

946 See also, FDA's Guidance to Industry, Changes to an Approved NDA or ANDA; Specifications
947 – Use of Enforcement Discretion for Compendial Changes, dated 11/19/2004 at
948 <http://www.fda.gov/cder/guidance/6451fnl.htm>.

949

950 **Compliance Policy Guides**

951

952 Sub Chapter 420 - Compendial /Test Requirements

953 Sec. 420.100 - Adulteration of Drugs Under Section 501(b) and 501(c) of the Act. *Direct
954 Reference Seizure Authority for Adulterated Drugs Under Section 501(b)* (CPG 7132a.03)

955

956 Any official drug which, when tested by compendial methods, fails to conform to compendial
957 standards for quality, strength, or purity, is adulterated unless the differences from such standards
958 are plainly stated on the drug's label.

959

960 Sec. 420.200 - Compendium Revisions and Deletions (CPG 7132.02)

961

962 All official articles shipped prior to the date that the current *USP–NF* became official should be
963 in compliance with the official compendia in effect at the time of shipment.

964

965 Sec. 420.300 - Changes in Compendial Specifications and NDA Supplements (CPG 7132c.04)

966

967 Any change in the compendial specifications for an NDA drug will normally require the
968 submission of an NDA supplement.

969

970 Sec. 420.400 - Performance of Tests for Compendial Requirements on Compendial Products
971 (CPG 7132.05) [Section 420.400 presently is under revision by FDA]

972

973 Compendial methods need only be applied, as a batch release test, where a firm has made
974 specific commitments to do so (as in a new drug application), or where the official method is the
975 only appropriate test. Neither the *USP–NF* nor the CGMP regulations necessarily require a firm
976 to utilize, as a batch release test, the methods and procedures stated in the official compendia.

977 What is required is that official drug products conform to the appropriate compendial standards.

978 The manufacturer's specifications for standards of strength, quality and purity may be less
979 stringent in those cases in which the differences from the official standards are stated on the
980 product label.

981

982 Where an official product purports to conform to the standards of the *USP– NF* the manufacturer
983 must assure that each batch conforms to each monograph requirement. This assurance must be
984 achieved by appropriate means, including process validation and controls and end product
985 testing. Therefore, in some cases it may not be necessary for a manufacturer to test each batch
986 for each monograph requirement.

987

988 Sec. 420.500 - Interference with Compendial Tests (CPG 7132a.01)

989

990 A compendial drug product containing an added substance which interferes with the compendial
991 assay of the product would be adulterated under 501(b) of the Act.