

1 **PQRI SURVEY FINDINGS OF PHARMACEUTICAL EXCIPIENT**
2 **TESTING AND CONTROL STRATEGIES, USED BY EXCIPIENT**
3 **MANUFACTURERS, EXCIPIENT DISTRIBUTORS AND**
4 **DRUG PRODUCT MANUFACTURERS**
5

6 The Product Quality Research Institute (PQRI) conducted an open, publicly available electronic
7 survey of current excipient- control strategies of pharmaceutical excipient manufacturers,
8 excipient distributors and drug product manufacturers (excipient users) to gather information that
9 will:

- 10
- 11 • Assess the range of current industry practice for excipient quality control to comply with
12 applicable 21 Code of Federal Regulations (CFR), United States Pharmacopeia –
13 National Formulary (*USP-NF*), and harmonized general chapter(s) and monographs, of
14 European Pharmacopoeia (Ph. Eur.) and Japanese Pharmacopoeia (JP) requirements. The
15 excipient quality control strategies include excipient manufacturing controls, excipient
16 manufacturer monograph testing, excipient user monograph testing, excipient
17 manufacturer and distributor audits by drug product manufacturers, and use of alternate
18 analytical methods in testing of excipients;
 - 19 • Assess the use of reduced testing of excipients;
 - 20 • Assess availability and use of simple, reliable, extra-monograph excipient tests to
21 determine excipient processability; and
 - 22 • Assess excipient users’ need to meet global requirements, use of alternate methods in
23 meeting those requirements, and the impact of Pharmacopoeial Discussion Group (PDG)
24 harmonization.

25

26 Three surveys were developed by the PQRI Excipient Working Group to receive responses from
27 excipient manufacturers, excipient distributors, and drug product manufacturers. The objective
28 of the surveys was to gather information on “Excipient Control Strategies” used by drug product
29 manufacturers who manufacture, distribute and sell primarily in United States and also globally,
30 “prescription only” and “over the counter” drug products. The surveys could be completed
31 electronically by individuals belonging to the PQRI member organizations (<http://www.pqri.org>)
32 and other interested persons, in an anonymous manner. The survey period was from June 13,
33 2005 to October 14, 2005. A total of 212 responses were received; 180 drug product
34 manufacturers, 26 excipient manufacturers, and 6 distributors of pharmaceutical excipients. It
35 should be recognized that PQRI is a unique US-based organization, and that the survey is US-
36 based. Further, it is recognized that some responses received for the survey could be from
37 excipient manufacturers and drug product manufacturers who manufacture their products for
38 distribution and sale outside the United States. This report presents findings of the three surveys
39 and the analysis of survey responses. For the purposes of this report, the terms “excipient user”
40 and “drug product manufacturer” mean the same thing. In addition, the terms “broker”,
41 “supplier” and “vendor” denote the company providing the excipient ingredient to the drug
42 product manufacturer. This company may also be either the excipient manufacturer or excipient
43 distributor.

44

45 It is to be noted that “Subpart E – Control of Components and Drug Product Containers and
46 Closures of Title 21 Code of Federal Regulations Part 211 – Current Good Manufacturing

47 Practice for Finished Pharmaceuticals” apply to sampling, testing, release, and use of excipients
48 as drug product components. “21 CFR Part 211.84, Testing and approval or rejection of
49 components, drug product containers and closures” describes the sampling, examination and
50 testing, approval, and release of an excipient for use in the manufacturing of a drug product, by a
51 drug product manufacturer. 21 CFR 211.84(d) requirements (1) & (2) are, “(1) At least one test
52 shall be conducted to verify the identity of each component of a drug product. Specific identity
53 tests, if they exist, shall be used.”; “(2) Each component shall be tested for conformity with all
54 appropriate written specifications for purity, strength, and quality. In lieu of such testing by the
55 manufacturer, a report of analysis may be accepted from the supplier of a component, provided
56 that at least one specific identity test is conducted on such component by the (drug product)
57 manufacturer, and provided that the (drug product) manufacturer establishes the reliability of the
58 supplier's analyses through appropriate validation of the supplier's test results at appropriate
59 intervals.” Additional regulatory requirements that may also apply can be found at
60 <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=211&showFR=1&subpartNode=21:4.0.1.1.10.5>¹.
61

62
63 The *USP-NF General Notices*², under Tests and Assays states that “Every compendial article in
64 commerce shall be so constituted that when examined in accordance with these assay and test
65 procedures, it meets all of the requirements in the monograph defining it. However, it is not to be
66 inferred that application of every analytical procedure in the monograph to samples from every
67 production batch is necessarily a prerequisite for assuring compliance with Pharmacopeial
68 standards before the batch is released for distribution. Data derived from manufacturing process
69 validation studies and from in-process controls may provide greater assurance that a batch meets
70 a particular monograph requirement than analytical data derived from an examination of finished
71 units drawn from that batch. On the basis of such assurances, the analytical procedures in the
72 monograph may be omitted by the manufacturer in judging compliance of the batch with the
73 Pharmacopeial standards.”
74

75 **Survey Highlights**

- 76
- 77 • Nearly all respondents (99%) stated that their excipient specifications comply with *USP-NF*
- 78 monograph requirements.
- 79 • Almost all drug product manufacturers (97%) test excipients according to *USP-NF*
- 80 monograph/general chapter methods; and approximately 1 in 6 excipient manufacturers and
- 81 excipient distributors do not.
- 82 • Most (79%) respondents (excipient manufacturers, excipient distributors, and excipient
- 83 users) have been inspected by the Food and Drug Administration (FDA); and most
- 84 distributors have been inspected by their State or Local Authorities.
- 85 • Most excipient specifications are both national (*USP-NF*) and global, versus up to 15% just
- 86 national (*USP-NF*).
- 87 • Most excipients obtained from new vendor sources are qualified by vendor audit (91%) and
- 88 complete testing according to compendial monograph (96%) for the article. An excipient

¹ An FDA search engine “Search CFR Title 21 Database” is at
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm>

² *USP—NF General Notices*, section Tests and Assays under Procedures.

89 from a new supplier (or vendor), is qualified approximately 35% of the time by supplier’s
 90 analytical method, about 50% by an in-house method, 63% of the time by process validation
 91 in the dosage form, but rarely (15%) accepted on Certificate of Analysis (C of A) with
 92 identity test alone.

- 93 • Greater than 70% of all respondents perform additional functionality or processability
 94 testing, 76% to determine excipient suitability, 66% always for the excipient, and little over
 95 50% for oral solutions. Such testing is done 87% of the time for solid oral dosage forms.
- 96 • Most drug product manufacturers (85%) and all distributors have a vendor certification
 97 program. Drug product manufacturers audit excipient manufacturing sites (87%) and testing
 98 sites (87%). Most audits performed by drug product manufacturers are done “on-site of the
 99 vendor” by their own company auditors (greater than 90%), less than 20% by third party, and
 100 53% of the audits include a questionnaire.

101

102 **Surprises**

103

- 104 • About 25% of the time drug product manufacturers test excipient suitability for processing,
 105 using experimental (laboratory) scale batches, or pilot scale manufacturing batches. This was
 106 higher than expected.
- 107 • When qualifying a new source of an existing excipient, batches were rarely (15%) accepted
 108 on Certificate of Analysis (C of A) with identity test alone. This is an accepted approach in
 109 the CFR, and would be expected to be higher, especially with increasing batch-to-batch
 110 experience.
- 111 • Most excipient manufacturers and distributors that replied to the survey do label their
 112 excipients as compendial grade. This may not be reflective of the entire excipient
 113 manufacturers industry since most are chemical and food additive manufacturers and serve
 114 the Pharmaceutical industry with a very small amount of their overall business.
 - 115 - GMP requirements perceived as being too restrictive generally do not impact their
 116 decision;
 - 117 - Low demand for compendial grade generally does not impact their decision;
 - 118 - “Can not meet the compendial monograph” criteria generally does not impact their
 119 decision.

120

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154

155 **Background**

156 When the European Agency for the Evaluation of Medicinal Products³ and US Food and Drug
 157 Administration⁴ issued excipients guidance in 2003, industry predicted that they would have the
 158 unintended result of causing additional paperwork and excessive testing for excipient control
 159 strategies, without adding benefits. In addition, industry believed the guidance effectively
 160 eliminated generally accepted and common excipient control strategies.

161 FDA interpretation of ICH CTD language used in sections P.4 Control of Excipients⁴ required
 162 that manufacturers specify each method used for routine testing of excipients, unless the method
 163 is exactly that of the pharmacopeia and full monograph testing is performed.

164 Often a drug-product manufacturer has methods used internally that are shown to produce
 165 equivalent results to those in a pharmacopeia. Also, many manufacturers with global markets
 166 seek to eliminate redundant testing of the same property by selecting a single method shown to
 167 be capable of ensuring compliance with requirements of many pharmacopeias. The United States
 168 Pharmacopeia has been clear that alternate methods are acceptable to demonstrate compliance
 169 with *USP—NF* requirements.⁵

³ European Agency for the Evaluation of Medicinal Product, "Note for Guidance on Excipients, Antioxidants and Antimicrobial Preservatives in the Dossier for Application for Marketing Authorisation of a Medicinal Product (CPMP/QWP/419/03)", February 20, 2003

⁴ US Food and Drug Administration, "Guidance for Industry, Drug Product: Chemistry, Manufacturing, and Controls Information" (January 2003), now withdrawn, Fed Reg 71(105), 31194-31195 (June 1, 2006)

⁵ *USP—NF* General Notices, section Tests and Assays under Procedures.

170 FDA recently announced its "Guidance for Industry on Chemistry, Manufacturing, and Controls
171 Information; Withdrawal and Revision of Seven Guidances"⁶. By focusing on the
172 Pharmaceutical *Current Good Manufacturing Practices (CGMPs) for the 21st Century* (CGMP
173 Initiative) and ICH Guidelines, FDA has strategically reduced industry's regulatory and
174 paperwork concerns, and changed the regulatory focus to concentrate on those aspects of
175 manufacturing that pose the greatest risk to the quality of the product. Although excipients
176 constitute a large portion of most drug products, they have been viewed as a low-risk aspect of
177 drug-product safety. They are, however, a key aspect of product Quality by Design (QbD).

178

179 **Definitions**

180

181 Drug Product – A finished dosage form, for example, tablet, capsule, or solution, that contains an
182 active ingredient, generally with excipients, that has been prepared for consumer use and that has
183 undergone all stages of production including packaging and labeling.

184

185 Excipient – Substances other than the active pharmaceutical ingredient, which have been
186 appropriately evaluated for safety and are included in a dosage form or drug delivery system to
187 either aid the processing of the drug product during its manufacture, protect, support or enhance
188 stability, bioavailability, or patient acceptability, assist in product identification, or enhance any
189 other attribute of the overall safety and effectiveness of the drug product during storage or use.

190

191 Excipient Distributor – The broker or agent that receives the excipient, and transfers it to other
192 brokers, agents, or excipient users. The excipient may be repackaged by the distributor.

193

194 Excipient Manufacturer – The organization that produces or manufactures the excipient.

195

196 Excipient User – The Drug Product Manufacturer that receives the excipient once it has left the
197 control of the excipient manufacturer, broker, or agent. The organization uses the excipient to
198 manufacture a drug product.

199

200 **Requirements That Apply To Use Of Excipients In Drug Products**

201

202 References to sections of Federal FD&C Act, FDA Regulations, FDA Guidances, FDA Draft
203 Guidances, ICH Guidelines and USP General Notices include:

204

- 205 A. Section 201(g)(1) of Federal FD&C Act, Definition of the term Drug.
206 (<http://www.fda.gov/opacom/laws/fdcact/fdcact1.htm>. Scroll down to g(1) to see the
207 definition of Drug.)
- 208 B. Part 211.84 of Title 21 CFR, Testing and approval or rejection of components, drug
209 product containers, and closures.
210 (<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm> and type 211.84
211 in the first search box to look at the regulations)

⁶ US Food and Drug Administration, "Guidance for Industry on Chemistry, Manufacturing, and Controls Information; Withdrawal and Revision of Seven Guidances," Federal Register 71(105), 31194-31195 (June 1, 2006).

- 212 C. FDA's Changes to an Approved NDA or ANDA Guidance, dated April 2004.
213 (<http://www.fda.gov/cder/guidance/3516fnl.pdf>;
214 <http://www.fda.gov/cder/guidance/4163fnl.pdf>;
215 <http://www.fda.gov/cder/guidance/6451fnl.pdf>);
- 216 D. FDA's Drug Product Guidance, Chapters II and III, Drug Products (NDAs and ANDAs)
217 and Investigational Formulations (INDs), dated February 1987.
218 (<http://www.fda.gov/cder/guidance/old029fn.pdf>)
- 219 E. FDA's "Draft Guidance for Industry on Drug Product; Chemistry, Manufacturing, and
220 Controls Information"; Dated January 2003.
221 (<http://www.fda.gov/cder/guidance/1215dft.pdf>)
- 222 F. FDA's "Guidance for Industry on Chemistry, Manufacturing, and Controls Information;
223 Withdrawal and Revision of Seven Guidances," Federal Register 71(105), 31194-31195,
224 dated June 1, 2006.
- 225 G. ICH Q6A Guideline, Test Procedures and Acceptance Criteria for New Drug Substances
226 and New Drug Products: Chemical Substances, published in 65 FR 251, Pages 83041 to
227 83063, December 29, 2000. (<http://www.fda.gov/OHRMS/DOCKETS/98fr/122900d.pdf>)
- 228 H. USP and NF General Notices and Requirements, such as those under "Tests and Assays",
229 "Official and Official Articles" and "Ingredients and Processes" published in the Official
230 USP-NF. (<http://store.usp.org/>)

231
232 **CURRENT INDUSTRY PRACTICES FOR EXCIPIENT CONTROL TO COMPLY**
233 **WITH APPLICABLE 21 CFR REGULATIONS, USP-NF AND HARMONIZATION**
234 **MONOGRAPH REQUIREMENTS**

235
236 **RESPONSES FROM EXCIPIENT MANUFACTURERS, EXCIPIENT DISTRIBUTORS,**
237 **AND DRUG PRODUCT MANUFACTURERS (EXCIPIENT USERS)**

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239 **Demographics of survey respondents**

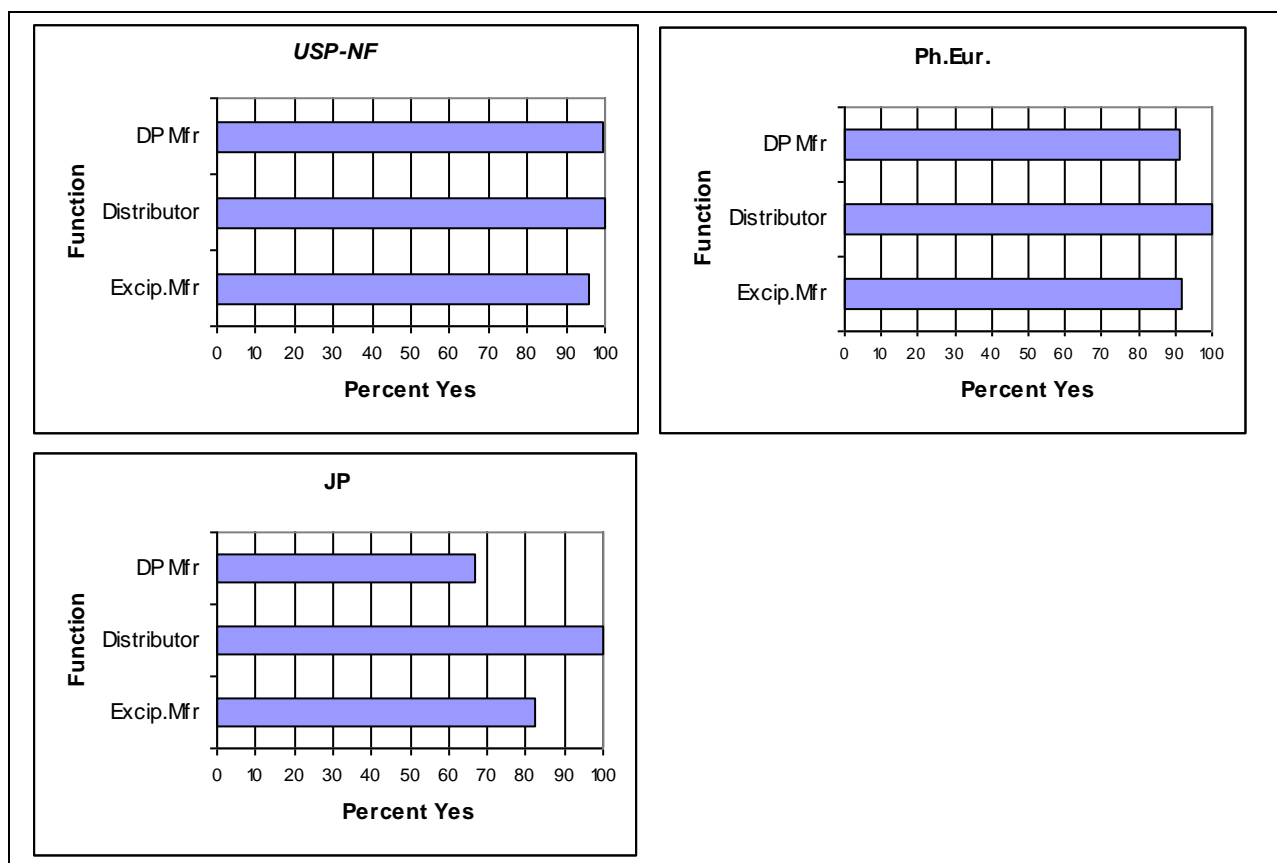
240
241 Majority (89%) of excipient manufacturers and drug product manufacturers operate as
242 multinational companies and sell their products in US, and 10% operate as a regional (US)
243 company. While 82% or more of their products are sold in US and globally, 11% are sold in US
244 only, and 7% exported outside the US.

245
246 If a company is multinational, 92% or more excipient manufacturers and drug product
247 manufacturers manufacture their products for different global regions, and 8% or less align their
248 products for a nation or a region. In the case of distributors, 80% distribute for global regions
249 from one site, and 20% align their site to a nation or region.

250
251 **Compliance with Pharmacopeial monograph requirements**

252
253 Most excipient specifications are both national and global (*USP-NF*, Ph.Eur., JP), and 10-15%
254 just national. Almost all (99%) respondents indicated that their excipient specifications comply
255 with *USP-NF*, 92% comply with Ph.Eur., and 83% comply with JP.

257 A large majority, 97% of drug product manufacturers test their excipients according to *USP-NF*
 258 monograph/General Chapter methods. About 16% of excipient manufacturers and distributors
 259 do not test their products according to *USP-NF* monograph/General Chapter methods.
 260



261
 262
 263 **Figure 1: Compliance with Compendial Requirements**

264
 265 Note in all graphs and figures DP Mfr = Drug Product Manufacturer; and Excip. Mfr = Excipient
 266 Manufacturer.

267
 268 **Verification of Excipient Quality by Drug Product Manufacturers**

269
 270 When excipient quality is verified by a drug product manufacturer, most use a compendial
 271 method or an in-house method. Nearly all (168 out of 169 responses) respondents stated that
 272 their excipient specifications comply with *USP-NF* requirements, and slightly less (92%) comply
 273 with European Pharmacopoeia.

274
 275 Almost all (97%) drug product manufacturers test their excipients according to *USP-NF*
 276 monograph/general chapter methods.

277
 278 When an excipient manufacturer has been audited, qualified, and has performed all tests
 279 according to compendia, or as approved in a drug product application, 49% of drug product
 280 manufacturers accept the material by performing ID test only (per 21 CFR 211.84) along with
 281 the manufacturer's C of A. Almost all (97%) drug product manufacturers perform more than just

282 the ID test before accepting an excipient. This clearly indicates that drug product manufacturers
 283 perform more testing on excipients they receive from their suppliers than minimally required by
 284 US FDA regulations. This finding also demonstrates drug product manufacturers' awareness
 285 and efforts to perform such additional testing towards successfully manufacturing their drug
 286 product batches.

287
 288 Less than 20% of drug product manufacturers accept material based on excipient manufacturer's
 289 process controls and in-process tests not mentioned on C of A, but providing assurance of *USP-*
 290 *NF* requirements. This is an area where opportunities exist for excipient manufacturers and drug
 291 product manufacturers to research and subsequently utilize information and knowledge that lies
 292 in the "manufacturing process-controls" and "in-process test results" domain of an excipient
 293 manufacturer. Assessment of such information could also confirm or otherwise indicate certain
 294 physicochemical quality aspects of an excipient batch, or qualities of excipient produced under
 295 continuous manufacturing conditions.

296
 297 About 74% of drug product manufacturers answered few or none for testing excipient suitability
 298 using experimental scale (laboratory scale) drug product lots or pilot scale manufacturing
 299 batches. This fact is not encouraging. Such a high number may be contributing to difficulties
 300 and/or surprises currently encountered by drug product manufacturers during production batch
 301 scale-up operations, or when an excipient is procured from different vendor(s).

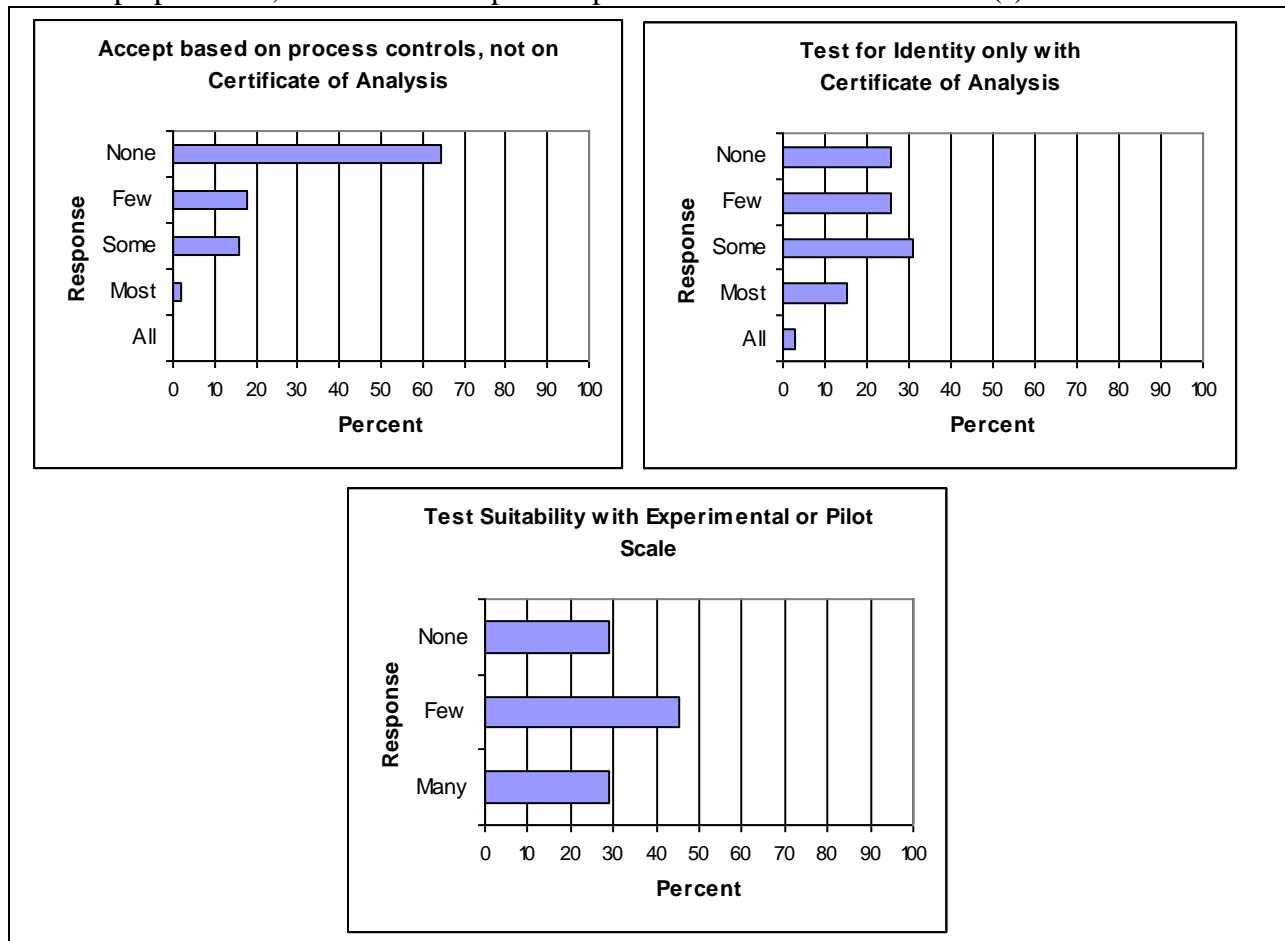


Figure 2: Verification of Excipient Quality

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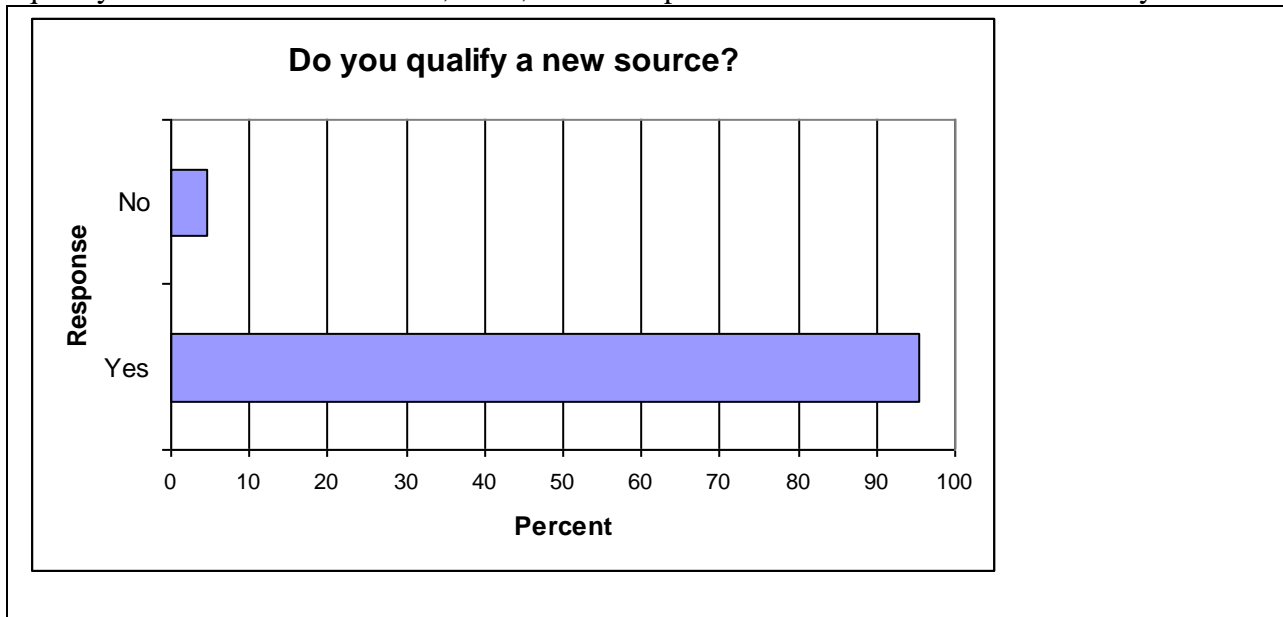
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Qualification of new sources of excipients by Drug Product Manufacturers

New sources of excipients currently used by a drug product manufacturer are almost always qualified, said 95% of respondents (102 out of 107). Such qualification occurs by vendor audits (91%). Complete testing of the excipient according to a compendial monograph (*USP-NF*, Ph.Eur., JP) is done by many of the respondents (96%) for some to all of the excipients while qualifying a new source. Rarely is a new vendor’s excipient qualified by testing according to the new supplier’s analytical method (6 out of 93 responses answered “all”). One third of the respondents do not use any of the supplier’s analytical methods while qualifying a new source of the excipient.

Up to 47% indicated the use of in-house analytical methods for qualifying a new source of vendor, for some to all of their excipients. Most (63%, or 60 out of 96) drug product manufacturers stated that a new vendor’s excipient is qualified via (their drug product manufacturing) process validation, with the new source of excipient in the dosage form (for some, most or all of the excipients).

Majority (85%, 82 out of 97) of drug product manufacturers do not qualify a new source of excipient based on C of A and an identity test only. Only 15% of respondents indicated they qualify their new source of some, most, or all excipients based on C of A and an identity test.



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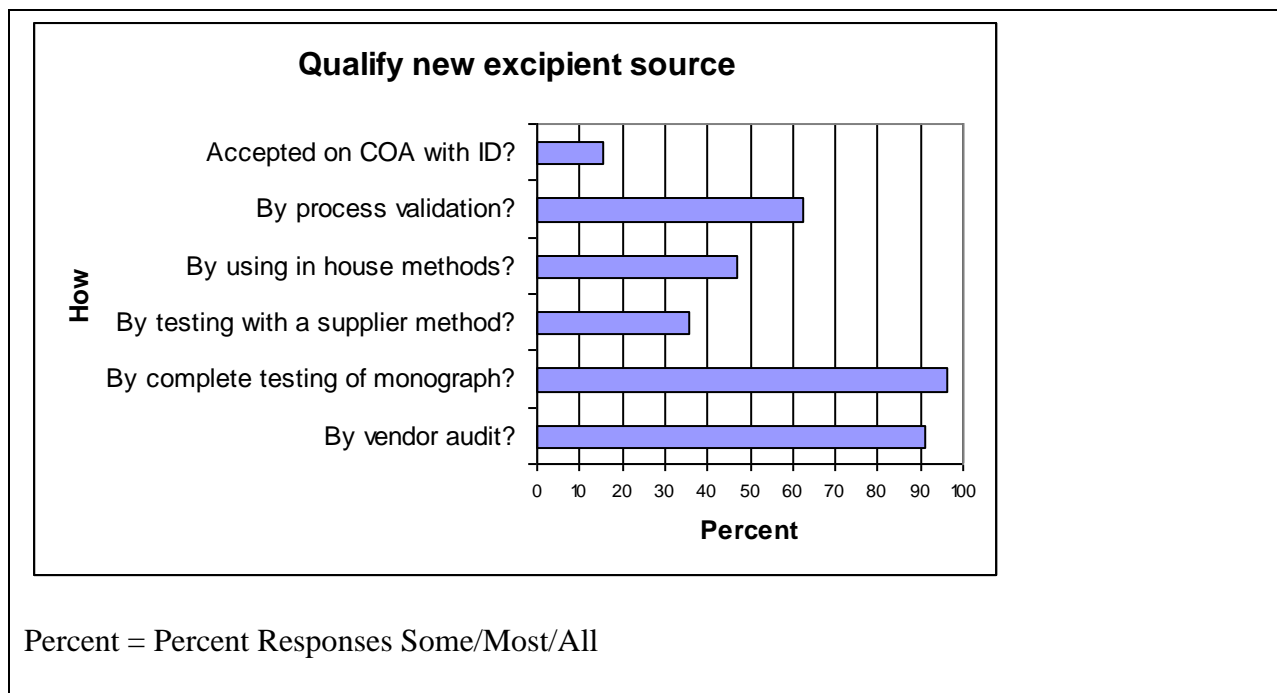


Figure 3: Qualify New Excipient Source

Difficulty in finding a manufacturer of USP-NF Grade excipients

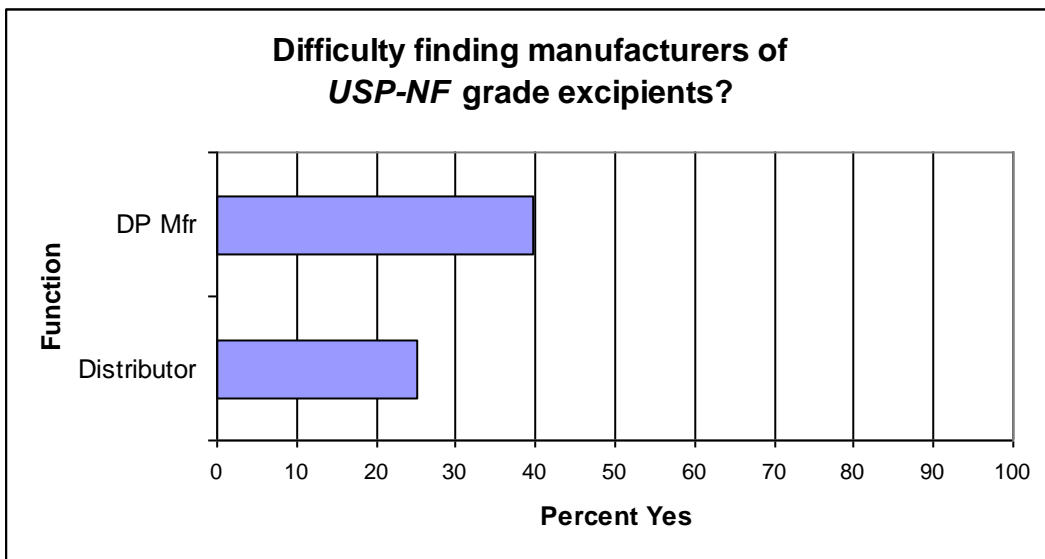
Approximately 40% of drug product manufacturers (41 out of 103), and 1 out of 4 distributors reported that they had difficulty in finding a manufacturer of USP-NF grade excipient. When such difficulty is experienced, the responses indicated that the distributor would “test” the available “noncompendial” labeled (also called as “noncompendial grade” for the purposes of this report) excipient according to a USP-NF monograph, and continue to supply or distribute the best grade available. Similarly, 75% of the drug product manufacturers (30 out of 40) also test a “noncompendial grade excipient” according to the USP-NF monograph. When the distributor and the drug product manufacturers do so, majority of them (85%) would also conduct an excipient manufacturer assessment, in addition to testing the excipient according to the USP-NF monograph.

When drug product manufacturers had difficulty in finding a supplier of USP-NF grade excipient, 61% (38 out of 62) indicated they have used excipients which were not labeled to be of compendial grade.

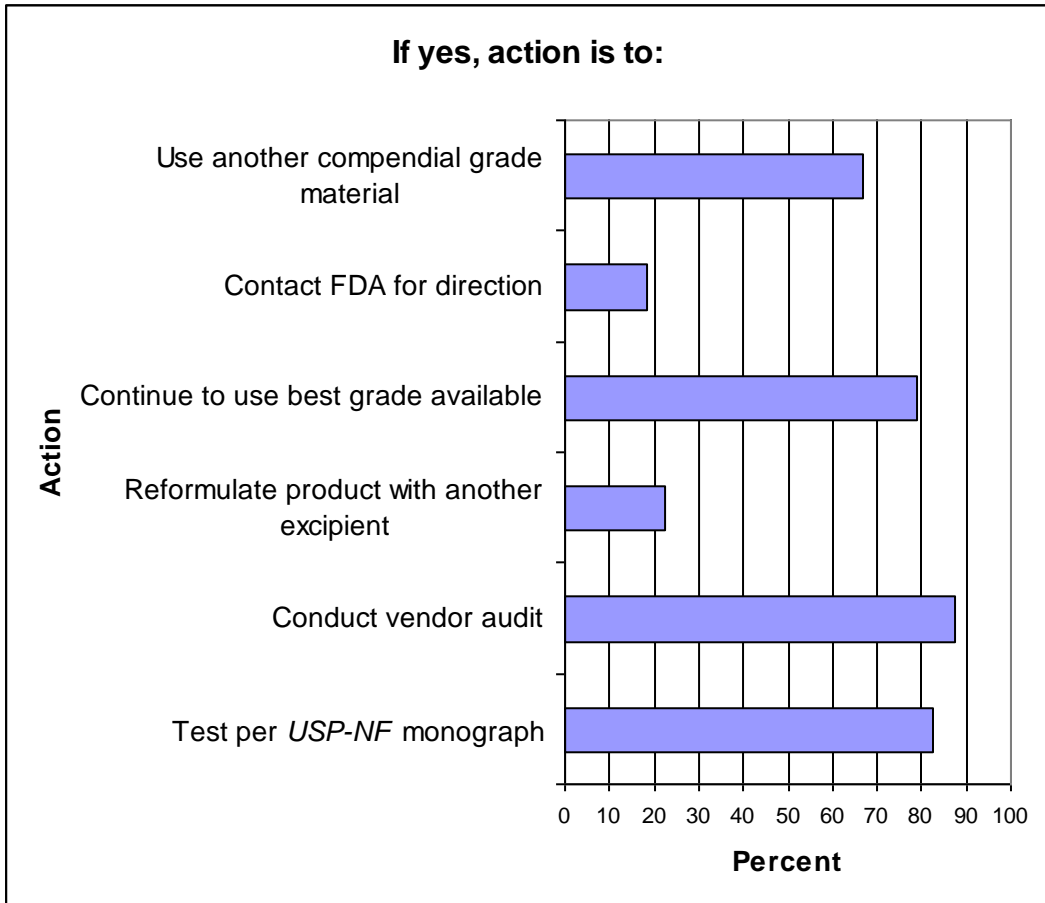
When noncompendial grade excipient is used, 78% of respondents (28 out of 36 answered none or few) did not reformulate their product with another excipient. They continued to use the best grade of excipient available.

When the distributors and drug product manufacturers experience difficulty in finding a USP-NF grade excipient, a majority of them (90%) do not choose to contact FDA for direction. Nearly 67% of the time, they indicated the use of another compendial (Ph.Eur., JP) grade excipient.

359 One out of six distributors, and 82% (75 out of 91) drug product manufacturers provided (or had)
 360 services for testing excipients according to compendia.
 361



362
 363



364
 365
 366

Percent = Percent Responses Some/Most/All

Figure 4: Difficulty finding Manufacturer of USP-NF grade excipient

367
368 **Testing of a noncompendial grade excipient to conform to compendial grade by testing and**
369 **manufacturing site audit**
370

371 One out of two distributors and 25% (20 out of 80) of drug product manufacturers do not
372 perform testing of a noncompendial grade excipient to conform to compendial quality. The
373 remaining 75% drug product manufacturers indicated they test (few to all) excipients to conform
374 to compendial grade. When they do so, 75% among them also performed excipient
375 manufacturer's site audits (some, most, or all the time).

376
377 Up to 90% of excipients procured as non-compendial grade from the excipient manufacturer are
378 tested by drug product manufacturers to determine if they conform to compendial quality. In this
379 situation, the excipient manufacturer is usually audited by the drug product manufacturer as
380 reported below in "Audit of excipient manufacturer and testing sites by Drug Product
381 Manufacturers." Only one distributor indicated that for a few excipients they tested non-
382 compendial grades to conform to compendial quality.

383
384 When a non-compendial grade excipient is tested to show conformance to compendial
385 requirements, the Certificate of Analysis is issued by the "Distributor" or the "testing laboratory"
386 up to 76% of the time (few to all excipients).

387
388 **Conformance of a compendial excipient to multi-compendial grade by testing**
389

390 The survey found that 55% of drug product manufacturers (43 out of 78) did not indicate
391 conformance of a compendial grade excipient to multi-compendial grade by testing, and the
392 remaining 45% "test" some or all excipients to be of multi-compendial monograph quality. Only
393 9% of respondents indicated they outsource such testing, and 91% indicated that such testing is
394 performed both in-house as well as outsourced. In 80% of cases (55 out of 71) compendial
395 methods are used for a noncompendial grade excipient to conform to a compendial grade, or
396 from one compendial grade to multi-compendial grades.

397
398 It should be recognized that in many cases, testing performed on a non-compendial grade
399 excipient to compendial grade, or from one compendial grade to multi-compendial grade would
400 only indicate the excipient passed the tested attribute. Such practice may not indicate the
401 physical properties, certain impurities, and microbiological quality aspects of an excipient.
402 Therefore, the tested excipient should not be labeled as compendial grade(s) excipient because
403 there are other compendial requirements.

404
405 **Audit of excipient manufacturer and testing sites by Drug Product Manufacturers**
406

407 Most, 87% (85 out of 98 responses) of drug product manufacturers have audited their excipient
408 manufacturers (for some to all of their excipients). Most, 87% (76 out of 87) of them have
409 audited the excipient testing sites for some to all of their excipients.

410
411 While 25% of drug product manufacturers audit most or all of their excipient manufacturers
412 through site visits, nearly 50% have visited their excipient distribution chain for some, most or

413 all of their excipients. About one-fourth (27%) of drug product manufacturers have not visited
 414 their excipient distribution chain for auditing.

415
 416 About half (46%) of drug product manufacturers responded that they have audited their excipient
 417 agents for some, most, or all of their excipients, while 54% indicated they have audited few or
 418 none of their excipient agents.
 419

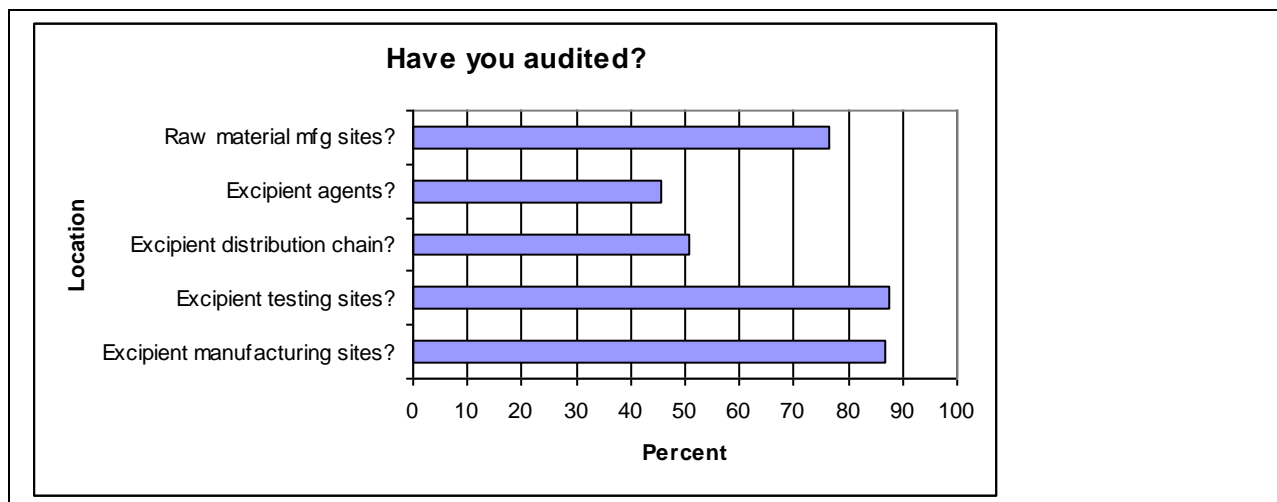


Figure 5: Excipient Audits

Frequency and method of auditing by Drug Product Manufacturers

420
 421
 422
 423 Frequency of audits performed by drug product manufacturers, of excipient manufacturer or
 424 supplier sites, excipient testing sites, excipient agents and excipient distribution chain are shown
 425 in Table 1.
 426
 427

428
 429 **Table 1: Drug Product Manufacturers Frequency of Audits**
 430

Excipient supply chain	# of respondents	Never	Every year	Every 2 years	Every 3-4 years	Every 5+ years
Manufacturer/supplier site	91	1	4	39	35	12
Testing site	81	5	18	32	17	9
Agent	68	23	3	10	16	16
Distribution chain	70	22	3	10	18	17

431
 432 Data shown in Table 1 above indicates that manufacturers audit their excipient manufacturers
 433 and excipient testing sites in most cases. One third (23 out of 68) of drug product manufacturers
 434 have not audited their excipient agents.
 435

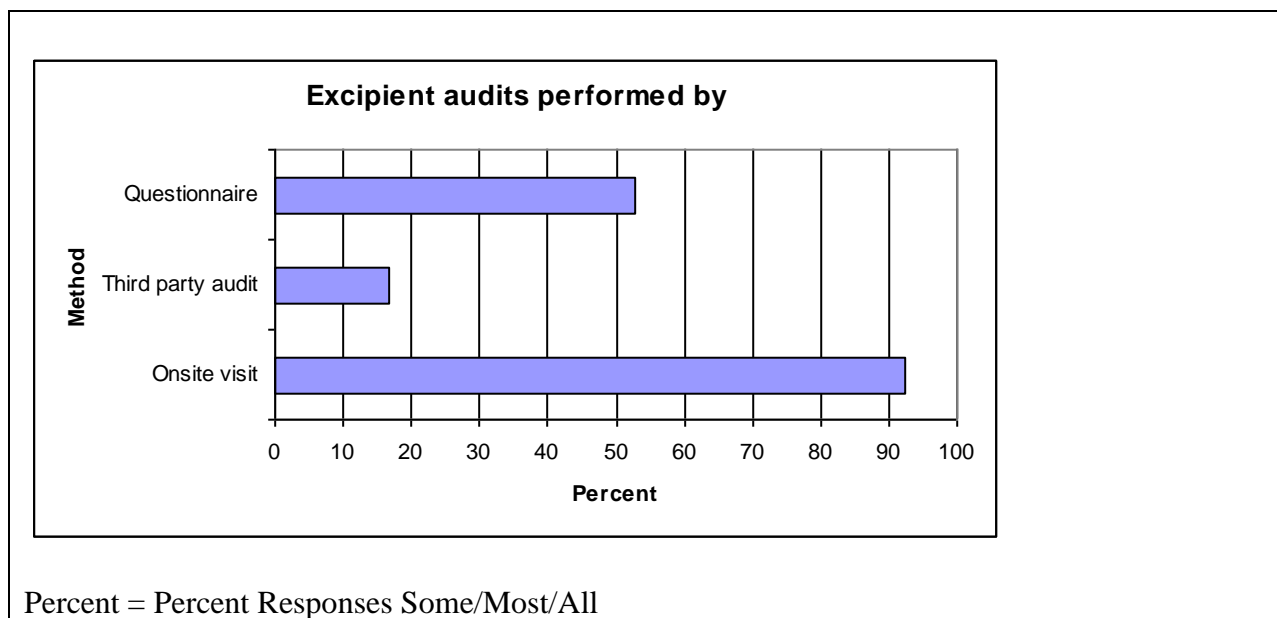
436 Methods used by drug product manufacturers for auditing the sites mentioned in Table 1 above
 437 are:

438
439

Table 2: Drug Product Manufacturers Audit Methods

Method used for Auditing	# of respondents	None	Few	Some	Most	All
Onsite visit by Company auditors	101	0	7	9	46	39
Third Party Audit	75	42	21	12	0	0
Questionnaire	85	17	23	14	8	23

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Figure 6: Audit Methods

448 On-site visit by a drug product manufacturer’s company auditor is the most common practice in
449 auditing an excipient manufacturer. Data in Figure 5 indicates that 87% of drug product
450 manufacturers have performed auditing of their excipient manufacturers for some to all of their
451 excipients. This is an opportunity to have third party auditors give an alternate view of the
452 excipient supplier, and reduce the number of independent audits of excipient suppliers.

453

Testing of excipients by alternate analytical methods having advantages over USP-NF

454

455
456 About 50% of excipient manufacturers and drug product manufacturers test excipients by
457 alternate analytical methods that have advantages over *USP-NF*, some or most of the time.

458

459 Alternate methods such as those published for Reagent Chemical, or by American Chemical
460 Society (ACS), or Association of Official Analytical Chemists (AOAC) are not used by 82% of
461 all survey respondents.

462

463 More than 50% of excipient manufacturers, excipient distributors, and drug product
464 manufacturers test excipients by alternate compendial methods including Ph.Eur. and JP.

465

466

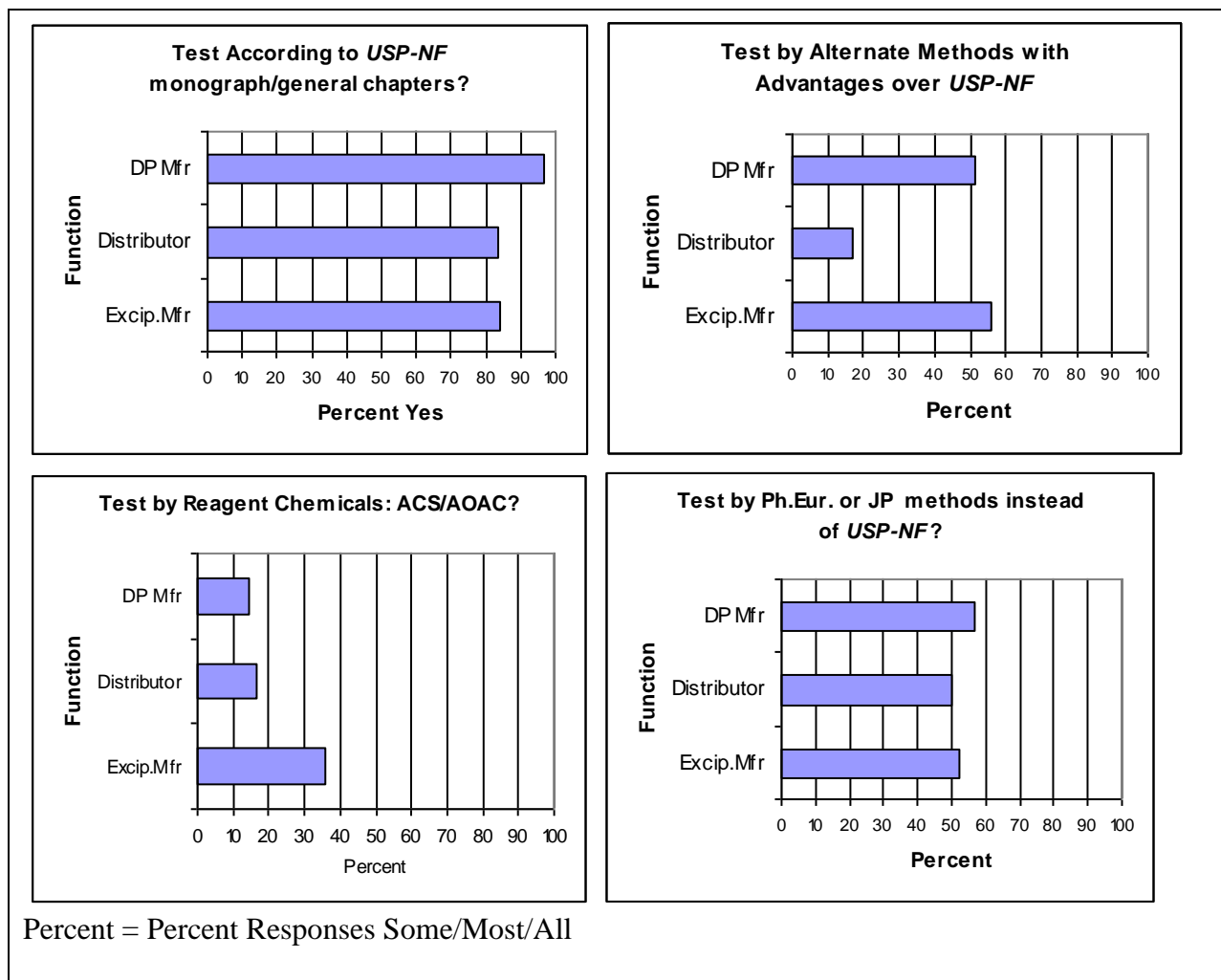


Figure 7: Alternative Analytical Methods

474 **TOPICS SPECIFIC TO EXCIPIENT MANUFACTURERS**

475 **Labeling of excipients as Compendial Grade**

476 Ten out of seventeen excipient manufacturers stated that they label most or all of their excipients
 477 as compendial grade. Five manufacturers labeled few or some excipients as compendial grade.
 478 Two manufacturers do not label their excipients as compendial grade.

481 Four out of five distributors stated that most or all of their excipients are labeled as compendial
 482 grade, and one distributor's products are not labeled as compendial grade.

483 The above findings indicate that most of the excipient manufacturers and distributors who
 484 responded to this survey label their excipients as compendial grade. However, it is noteworthy
 485 that 2 out of 17 (11%) excipient manufacturers and 1 out of 5 (20%) excipient distributors are
 486 not choosing to label their products as compendial grade. The reason(s) for not labeling their
 487
 488

489 excipients as compendial grade cannot be accurately determined from the responses to this
 490 survey. The authors have experienced a growing number of situations where excipient
 491 manufacturers are dropping the compendial grade label, i.e. USP, Ph.Eur., JP, either because of
 492 the increasing GMP expectations or the low volumes sold to the pharmaceutical market vs. the
 493 efforts required to meet pharmaceutical manufacturer's expectations. There are hundreds of
 494 excipient manufacturers and the survey was only answered by 26 excipient manufacturers.
 495 Therefore, this may not be reflective of the entire excipient manufacturing industry since most
 496 are chemical and food additive manufacturers and serve the pharmaceutical industry with a very
 497 small amount of their overall business.

498
 499 Five reasons were included in the survey that could impact an excipient manufacturer or
 500 distributor's decision to label their products as compendial grade. Excipient manufacturer's and
 501 distributor's responses to those scenarios are separately shown in Tables 3 and 4:
 502
 503

504 **Table 3: Excipient Manufacturer's Decision to Label**

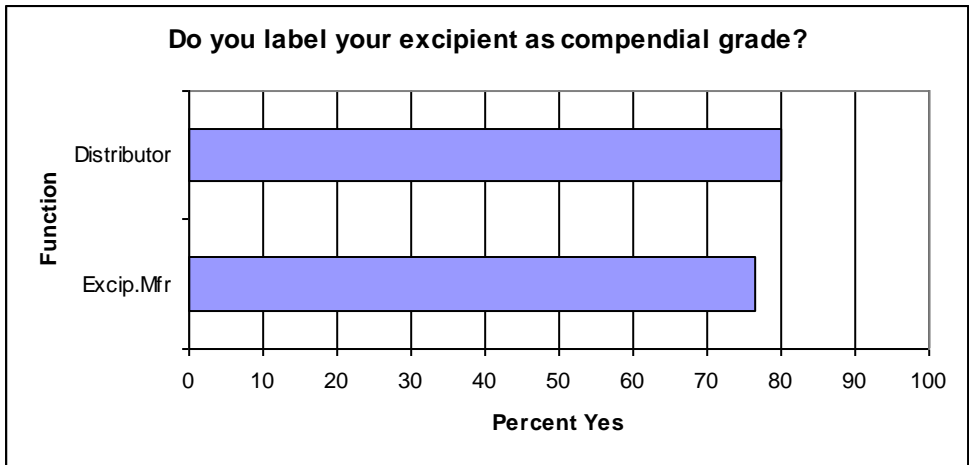
Manufacturer's decision impacted by:	None	Few	Some	Most	Total
GMP requirements are too restrictive	6	6	2	3	17
Low demand for compendial grade	6	5	2	4	17
Can't meet the compendial monograph	13	3	0	1	17
Potential to be inspected by FDA	10	2	4	1	17
Internal time/ resources required for Pharmaceutical Manufacturer Audits	7	5	2	3	17

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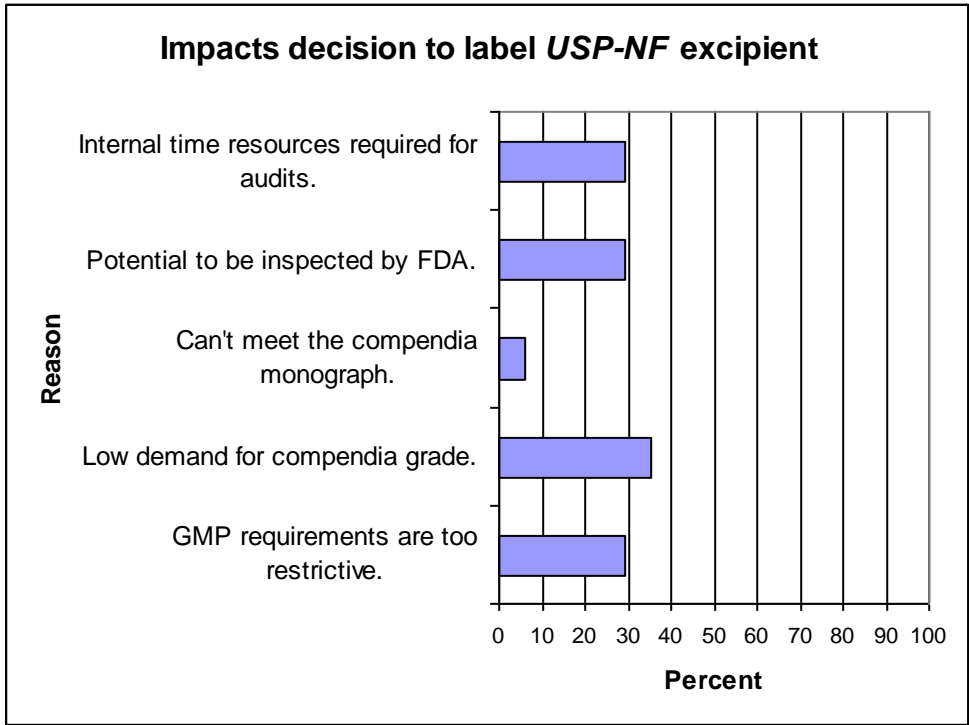
Table 4: Distributor's Decision to Label

Distributor's decision impacted by:	None	Few	Some	Most	Total
GMP requirements are too restrictive	4	0	0	0	4
Low demand for compendial grade	4	0	0	0	4
Can't meet the compendial monograph	3	0	1	0	4
Potential to be inspected by FDA	4	0	0	0	4
Internal time resources required for Pharmaceutical Manufacturer Audits	3	1	0	0	4

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Percent = Percent Responses Some/Most/All

Figure 8: Labeling

Audit of Excipient Manufacturers by Drug Product Manufacturers

520 Out of 17 excipient manufacturers who responded, 9 stated that most of their customers have
521 audited them, and 7 stated that some of their customers have audited them. Only one excipient
522 manufacturer stated that all of their customers have audited them. Most (13 of 17) stated that
523 their audits were by on-site visit of their “customer’s auditors” most of the time. Three excipient
524 manufacturers were visited by ‘some’ of their customers, and only one excipient manufacturer
525 stated that they were visited by ‘few’ of their customer’s auditors.

526
527 Third party audits and audits by questionnaire to excipient manufacturers by their customers are
528 shown in Table 5.

529
530 **Table 5: Audit Methods of Excipient Manufacturers**
531

Method used for auditing of an excipient manufacturer	# of respondents	None	Few	Some	Most	All
Third Party Audit	14	4	5	3	1	1
Customer's Questionnaire	17	1	4	8	3	1

532
533 Of the 17 excipient manufacturers' responses, 1 stated that, on average, they have on-site visit by
534 their customers every week. Of the remaining responses, 5 are visited by at least one customer
535 once in 2 weeks; 2 manufacturers are visited by their customers every 4 weeks and 8 weeks
536 respectively, and 7 stated that they have a customer at their site less often than every 8 weeks.

537
538 **Auditing of raw material suppliers by Excipient Manufacturers**
539

540 Of the 17 responses, 2 excipient manufacturers audited all of their raw material suppliers. Of the
541 remainder, 7 (41%) audited most, 4 (24%) some, 1 (6%) few, and 3 (18%) none of their raw
542 material suppliers.

543
544 **Industry standards used by excipient manufacturers, and desired by distributors and drug
545 product manufacturers**
546

547 Current practices of recommended industry standards developed and used by pharmaceutical
548 excipient manufacturers, and desired by distributors and drug product manufacturers are shown
549 in Table 6.

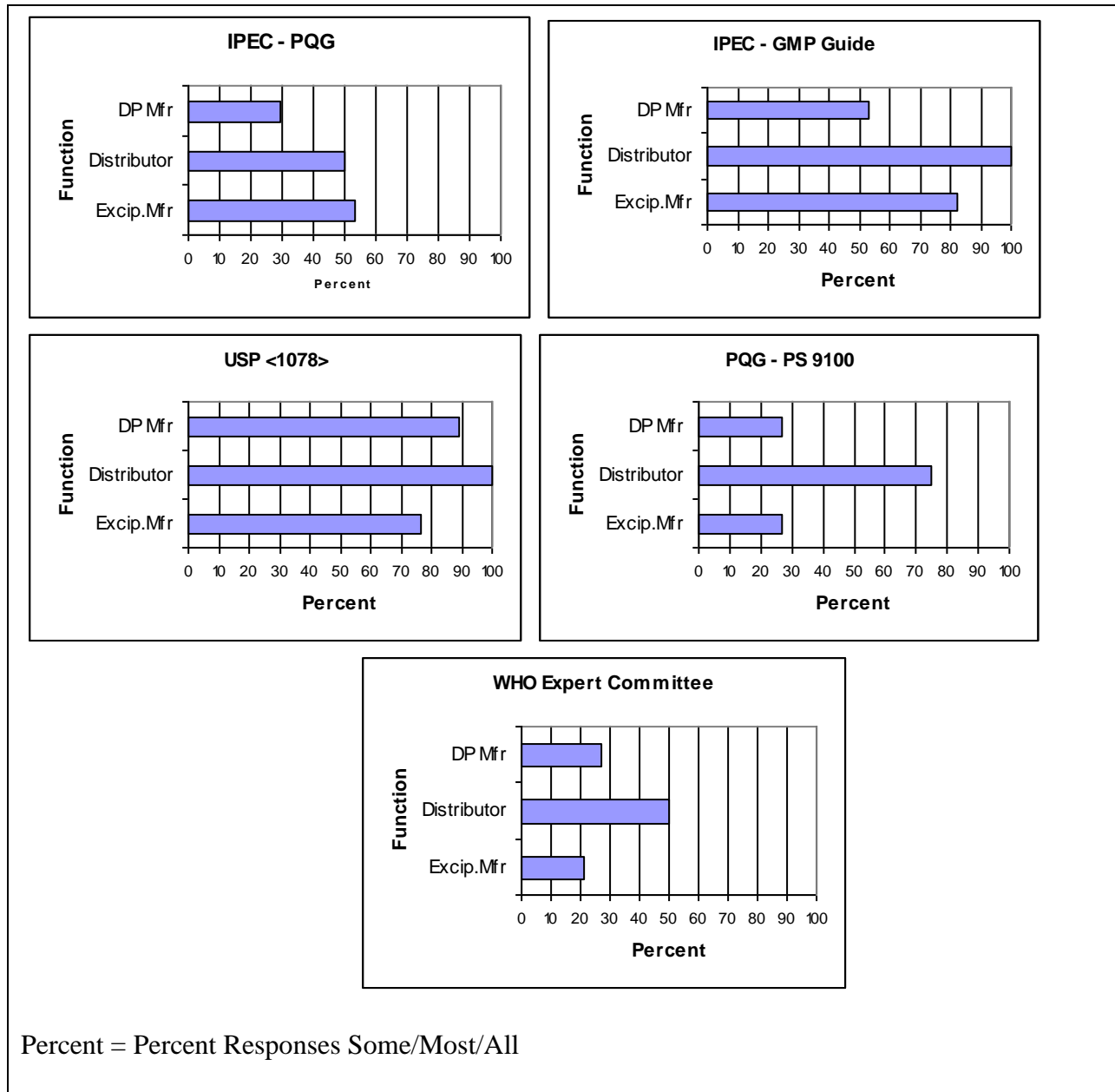
550
551 The USP General Information Chapter <1078> is the most commonly used voluntary industry
552 standard. Note that the original IPEC GMP is the basis of the *USP-NF* standard, and that a new
553 Joint IPEC-PQG Guide was launched January 26, 2006. It is expected that *USP-NF* will update
554 <1078> to align with the Joint IPEC-PQG Guide.
555

556
557**Table 6: Industry Standards**

Recommended voluntary industry standards used or desired	Excipient Manufacturers		Excipient Distributors		Drug Product Manufacturers	
	None, Few	Some, Most, All	None, Few	Some, Most, All	None, Few	Some, Most, All
(Note: Not all questions of the survey were answered by respondents)						
Total # of responses received	14 to 17		4 to 5		78 to 101	
International Pharmaceutical Excipients Council – Pharmaceutical Quality Group (IPEC-PQG) Guide	47%	53%	50%	50%	70%	30%
IPEC Good Manufacturing Practices Guide for Bulk Pharmaceutical Excipients 2001	18%	82%	0	100%	47%	53%
USP <1078> Good Manufacturing Practices (GMPs) for Bulk Pharmaceutical Excipients	24%	76%	0	100%	11%	89%
Pharmaceutical Quality Group (PQG) – PS 9100: 2002; “The application of ISO 9001: 2000 and GMP Guide for pharmaceutical excipients”	73%	27%	25%	75%	73%	27%
World Health Organization (WHO); WHO expert committee on Specifications for Pharmaceutical Preparations, 35 th Report, Geneva, WHO, 1999, Annex 5 (WHO Technical Series, No. 885; GMPs: Supplementary Guidelines for the manufacture of pharmaceutical excipients	79%	21%	50%	50%	73%	27%

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Figure 9: Industry Standards Used

563

564

565 Percent = Percent Responses Some/Most/All

566

567

568

569 **TOPICS SPECIFIC TO EXCIPIENT DISTRIBUTORS**

570

571 **Excipient manufacturer assessment before distributing the product**

572

573 All distributors (5 out of 5) and 85% (95 out of 112) of drug product manufacturers stated that
 574 they perform an excipient manufacturer assessment before distributing their products.

575

576

577

578 **Vendor certification and audit by Distributors**

579
580 The five distributors who responded all stated that they do perform an excipient manufacturer’s
581 assessment before distributing the product. The majority of their audits (4 of 5) occur by visiting
582 the vendor’s site. The distributors (4 respondents) all stated to have visited their excipient
583 suppliers and most have visited the excipient testing sites (4 of 5).
584

585 **Capability of distributors to handle or store an excipient due to stability concerns**

586
587 All 5 distributors stated to have adequate capability to handle or store the excipients to address
588 the respective excipient stability concerns. Half (50%, 2 of 4) of distributors did not have
589 adequate capability to handle or store excipients that needed frozen storage conditions. This may
590 not be a concern if the distributor does not have excipients needing these conditions.
591

592 **Frequency and method of auditing by Distributors**

593
594 Frequency of audits performed by distributors, of excipient manufacturer or supplier sites,
595 excipient testing sites, excipient agents and excipient distribution chain are shown in Table 7.
596

597 **Table 7: Audit Frequency by Distributors**

598

Excipient supply chain	# of respondents	Never	Every year	Every 2 years	Every 3-4 years	Every 5+ years
Manufacturer/supply site	4	0	1	1	2	0
Testing site	4	1	1	1	0	1
Agent	3	1	0	0	1	1
Distribution chain	3	2	0	0	0	1

599
600 Methods used by distributors for auditing the sites mentioned in Table 7 above are:

601 **Table 8: Audit Methods by Distributors**

602
603

Method used for auditing	# of respondents	None	Few	Some	Most	All
Onsite visit by Company auditors	5	1	0	2	1	1
Third Party Audit	3	2	0	0	1	0
Questionnaire	4	1	1	1	1	0

604
605
606 **Audit of Excipient Distributors by Drug Product Manufacturers**

607
608 Out of the 4 distributors who responded, 2 stated that some of their customers have audited them,
609 and the other 2 stated that most of their customers have audited them. One distributor stated that
610 their audits were by on-site visit of their customer’s auditors all the time. Two distributors stated
611 that drug product manufacturers audit them on-site most of the time, and one distributor stated
612 that they have on-site audit by their customers, some of the time.

613 Third party audits and audits by questionnaire to the distributors, by their customers are shown in
 614 Table 9.

615 **Table 9: Drug Product Manufacturer Audit Methods of Distributors**

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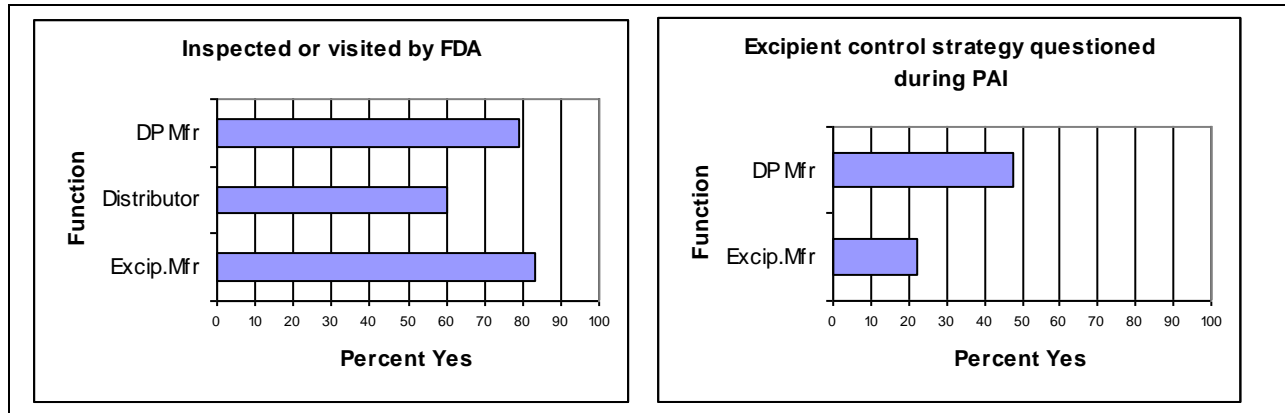
Method used for auditing of a distributor by their customers	# of respondents	None	Few	Some	Most	All
Onsite visit	4	0	0	1	2	1
Third Party Audit	3	3	0	0	0	0
Customer’s Questionnaire	3	0	1	1	1	0

617
 618 Of the 4 distributors who responded, 1 stated that, on average, they are visited by their customers
 619 once every 4 weeks, 1 distributor is visited by their customers every 8 weeks, and 2 stated that
 620 they have a customer at their site less often than every 8 weeks.

621
 622 **INSPECTIONS BY FDA, STATE AND LOCAL AUTHORITIES**

623
 624 Over 80% of excipient manufacturers (15 of 18), 79% of drug product manufacturers (94 out of
 625 119), and 3 out of 5 distributors indicated that they have been inspected by the FDA for either
 626 drug excipient or food use. The excipient control strategy of 22% (4 out 18) excipient
 627 manufacturers and 48% drug product manufacturers has been audited or questioned by the FDA
 628 during a pre-approval inspection (PAI). During a cGMP inspection, the excipient control
 629 strategy of 56% (10 out of 18) of excipient manufacturers and 58% (66 out of 114) drug product
 630 manufacturers has been audited or questioned by the FDA.

631
 632 Most distributors (4 of 5) indicated that they have been inspected or visited by State or Local
 633 authorities.



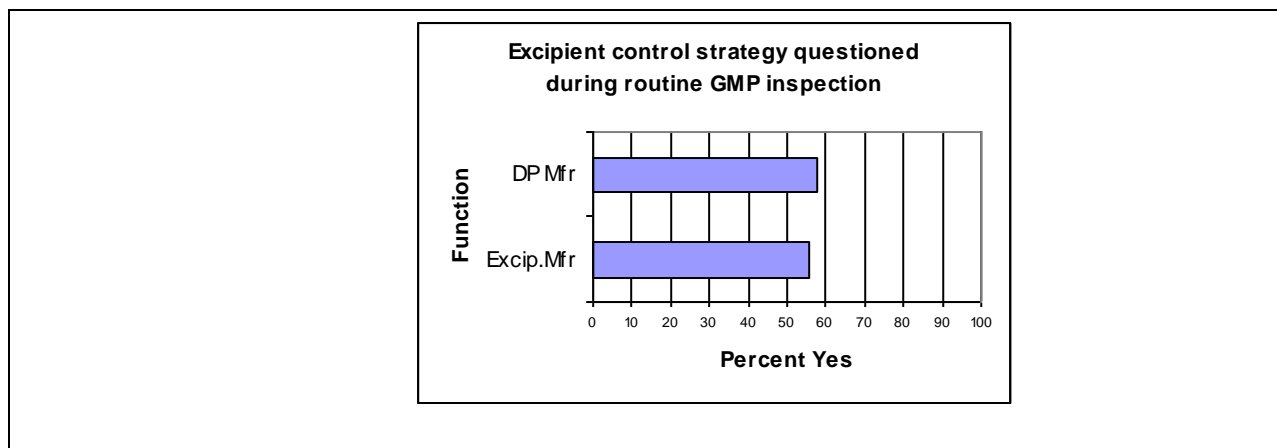


Figure 10: Inspections

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Familiarity with applicable FDA and compendial requirements and recommendations related to testing of excipients (components) used in a drug product

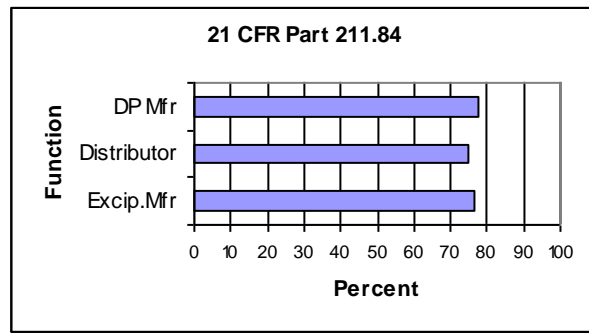
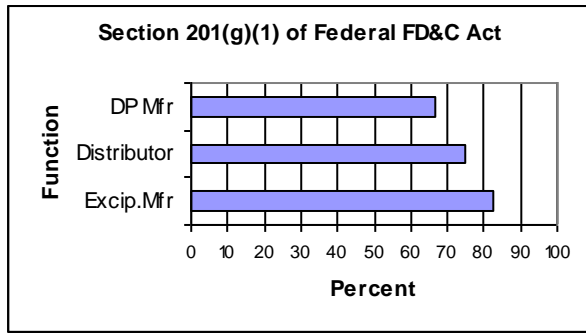
Table 10: Familiarity of Requirements

Applicable FDA and compendial requirements, and recommendations	Excipient Manufacturers		Excipient Distributors		Drug Product Manufacturers	
	No, or Some	Moderate, Very, or Complete	No, or Some	Moderate, Very, or Complete	No, or Some	Moderate, Very, or Complete
(Note: Not all questions of the survey were answered by respondents)						
Total # of responses received	16 to 17		4		101 to 106	
Section 201(g)(1) of the Federal FD&C Act, Definition of the term Drug	18%	82%	25%	75%	33%	67%
Title 21 CFR Part 211.84, Testing and approval or rejection of components, drug product containers and closures	24%	76%	25%	75%	22%	78%
FDA’s Changes to an Approved NDA or ANDA Guidance, dated April 2004	53%	47%	25%	75%	37%	63%
FDA’s Drug Product Guidance, Chapters II and III, Drug Products (NDAs and ANDAs) and Investigational Formulations (INDs), dated February 1987	59%	41%	25%	75%	44%	56%
FDA’s Draft Guidance for Industry on Drug Product; Chemistry, Manufacturing and Controls Information, dated January 2003	47%	53%	0	100%	34%	66%

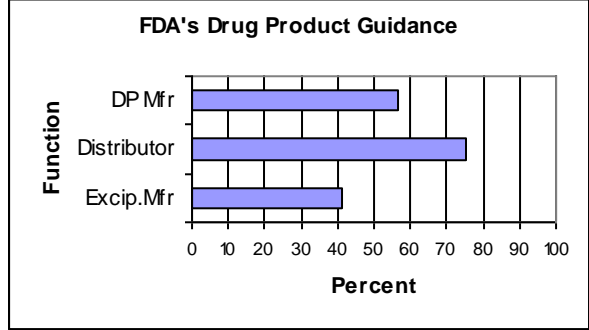
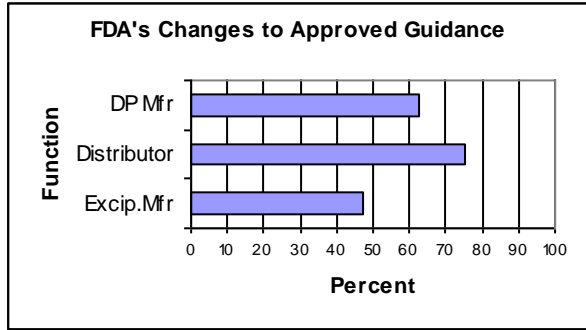
Applicable FDA and compendial requirements, and recommendations	Excipient Manufacturers		Excipient Distributors		Drug Product Manufacturers	
	No, or Some	Moderate, Very, or Complete	No, or Some	Moderate, Very, or Complete	No, or Some	Moderate, Very, or Complete
(Note: Not all questions of the survey were answered by respondents)						
Total # of responses received	16 to 17		4		101 to 106	
ICH Q6A Guideline, Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances, published in 65 FR 251, Pages 83041 to 83063, December 29, 2000	44%	56%	0	100%	27%	73%
USP and NF General Notices and Requirements, such as those under “Tests and Assays”, “Official and Official Articles” and “Ingredients and Processes” published in the Official <i>USP-NF</i>	12%	88%	25%	75%	11%	89%

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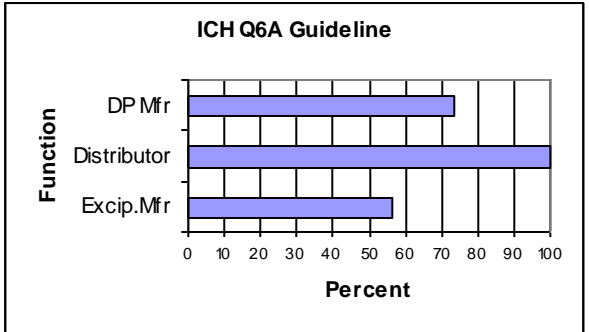
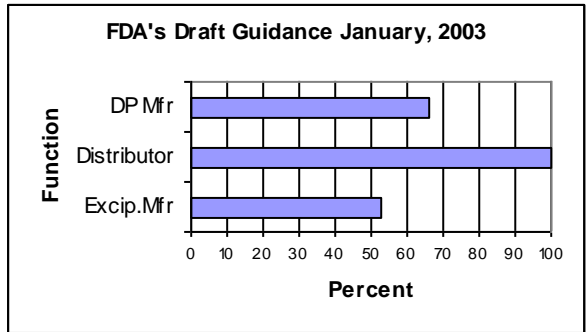
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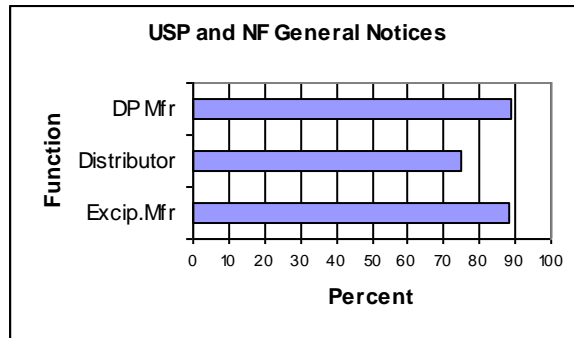
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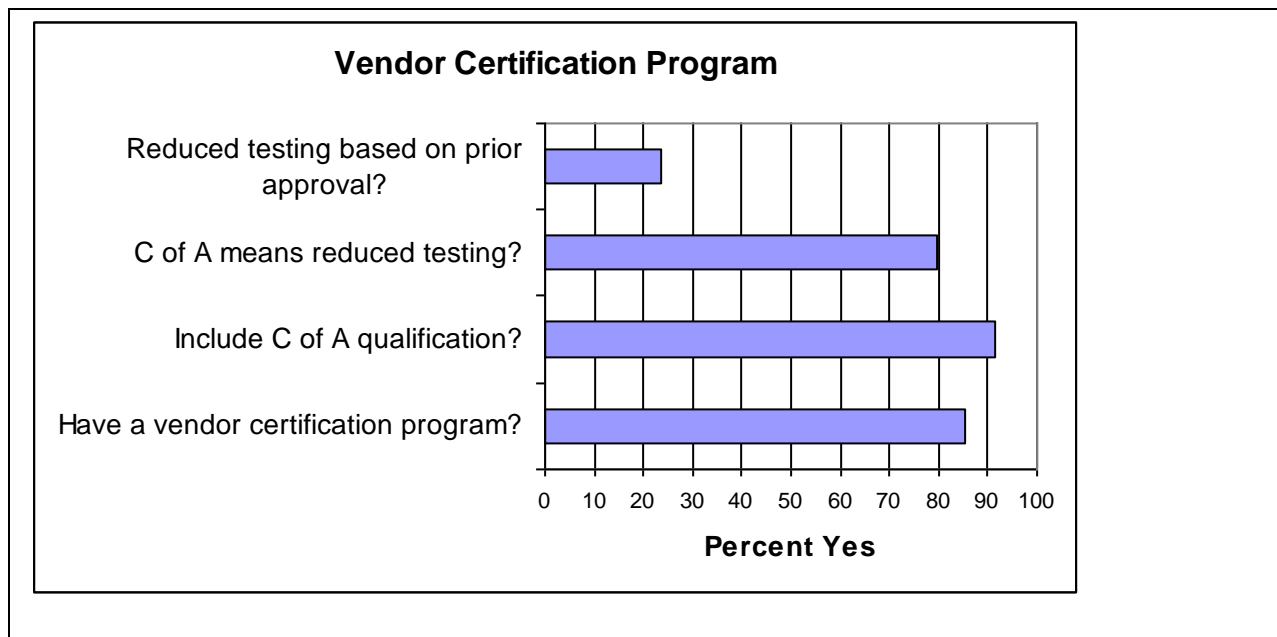


Percent = Percent Responses Moderate/Very/Completely Familiar

Figure 11: Familiarity with statutes, regulations, guidance and compendial requirements

659 **USE OF REDUCED TESTING**

660
 661 When asked about vendor qualification, 91% of drug product manufacturers stated that their
 662 vendor qualification includes Certificate of Analysis (C of A) qualification. For 78% of them
 663 (73 out of 93) such qualification of C of A means a reduced frequency of complete monograph
 664 testing for their excipients. For 24% (20 out of 85) respondents, such reduced frequency of
 665 testing is based on prior approval by the Food and Drug Administration (FDA).
 666



667
 668
 669 **Figure 12: Vendor Certification**

670
 671 The reduced testing programs for 89% of drug product manufacturers included at least 5 of their
 672 excipients. All five distributor respondents stated that a reduced testing program is applicable to
 673 some, most, or all of the products they distribute. This data suggest that many drug product
 674 manufacturers and excipient distributors do not perform complete monograph tests on their
 675 excipients after qualifying their vendors.
 676

677 Every 3rd lot of the excipient a drug product manufacturer receives is fully tested by 3% of them,
 678 every 5th lot by 7%, and every 10th lot by 29%, and the remaining 61% test their excipients
 679 according to “other” frequency (not specified above). The data suggest it is common to fully
 680 test every 10th lot.
 681

682 **AVAILABILITY AND USE OF ADDITIONAL, SIMPLE, RELIABLE EXTRA-**
 683 **MONOGRAPH EXCIPIENT TESTS**

684
 685 For *USP-NF* excipients, 88% of excipient manufacturers (14 out of 16), 75% of distributors (3
 686 out of 4), and 68% drug product manufacturers (75 out of 111) perform additional functionality
 687 or processability testing that is not part of any compendial monograph (*USP-NF*, Ph.Eur., JP).
 688 Over three-fourths (76%) of drug product manufacturer respondents perform such tests to
 689 determine excipient suitability for their intended use.

690

691 Most (12 out of 15) excipient manufacturers perform such tests always for the excipient, and 20%
692 of the time for one particular customer. Slightly fewer, (3 out of 5) distributors perform
693 additional testing always for an excipient and 40% for one particular customer. About two thirds
694 of drug product manufacturers (50 out of 78) perform additional testing always for an excipient,
695 and 36% perform such additional testing, for one particular product.

696

697 Additional functionality or processability testing is also done by drug product manufacturers; by
698 52% respondents for oral solution drug products, 87% for solid oral dosage forms, 45% for
699 topical/transdermal products, 56% for sterile/parenteral products, and 46% for inhalation/nasal
700 dosage forms.

701

702 In addition to performing functionality and processability related testing, additional testing which
703 is not part of a compendial monograph is also performed by drug product manufacturers because
704 of stability concerns (55%), processing concerns (87%) and impurity concerns (65%).

705

706 Survey responses presented in this section indicate that additional tests beyond those required by
707 compendial monograph are performed by the excipient manufacturers, distributors and drug
708 product manufacturers. Performing such tests by drug product manufacturer can contribute to
709 higher predictability and success in the overall processing, and in the quality of the finished drug
710 product.

711

712 **Where the additional tests are performed**

713

714 All excipient manufacturers and distributors stated that the additional testing is performed at the
715 excipient manufacturer's laboratory. Only 40% of drug product manufacturer respondents stated
716 that such additional tests are performed at the excipient manufacturer's laboratory.

717

718 Nearly all drug product manufacturers (74 out of 80) perform functionality and processability
719 related tests. About 52% of the time, such tests are conducted at a contract laboratory.

720

721 **Extra-monograph tests on excipients by Drug Product Manufacturer to assess its** 722 **processability**

723

724 A quarter (24%) of drug product manufacturers have products for which excipient variability is
725 still a problem in spite of performing pharmacopeial tests, and additional non-pharmacopeial
726 testing.

727

728 **Type of laboratory tests capable of showing processability or suitability of an excipient for** 729 **intended use**

730

731 The following percent of drug product manufacturers indicated performing extra-compendial
732 tests on the excipients they use:

733

- 734 ● 40% Sterility Tests
- 735 ● 66% Bacterial Endotoxins Test

- 736 • 84% Microbial Limit Tests
- 737 • 73% Viscosity Test
- 738 • 80% Moisture content test
- 739 • 64% Tap Density Test
- 740 • 73% Bulk Density Test
- 741 • 55% Particle shape/morphology tests
- 742 • 89% Particle size and size distribution test
- 743

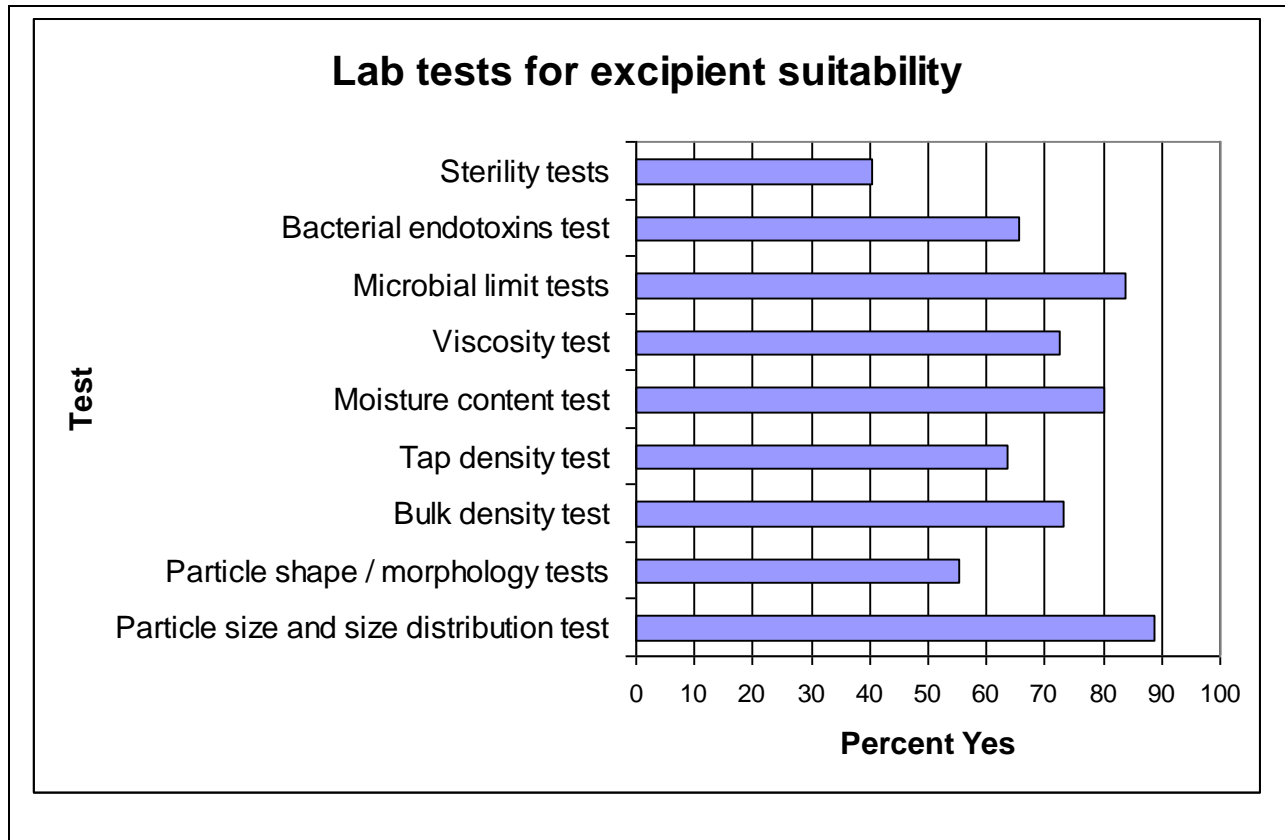


Figure 13: Tests for Suitability

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 746
 747
 748 Laboratory methods used for performing extra-compendial tests are:

- 749
- 750 • 51% Specific metals tests
- 751 • 23% AA graphite furnace
- 752 • 17% ICP
- 753 • 23% Laser light diffraction or scattering
- 754 • 22% X-ray diffraction
- 755 • 49% Near Infrared Spectroscopy
- 756 • 46% Microscopy
- 757 • 71% Sieving
- 758

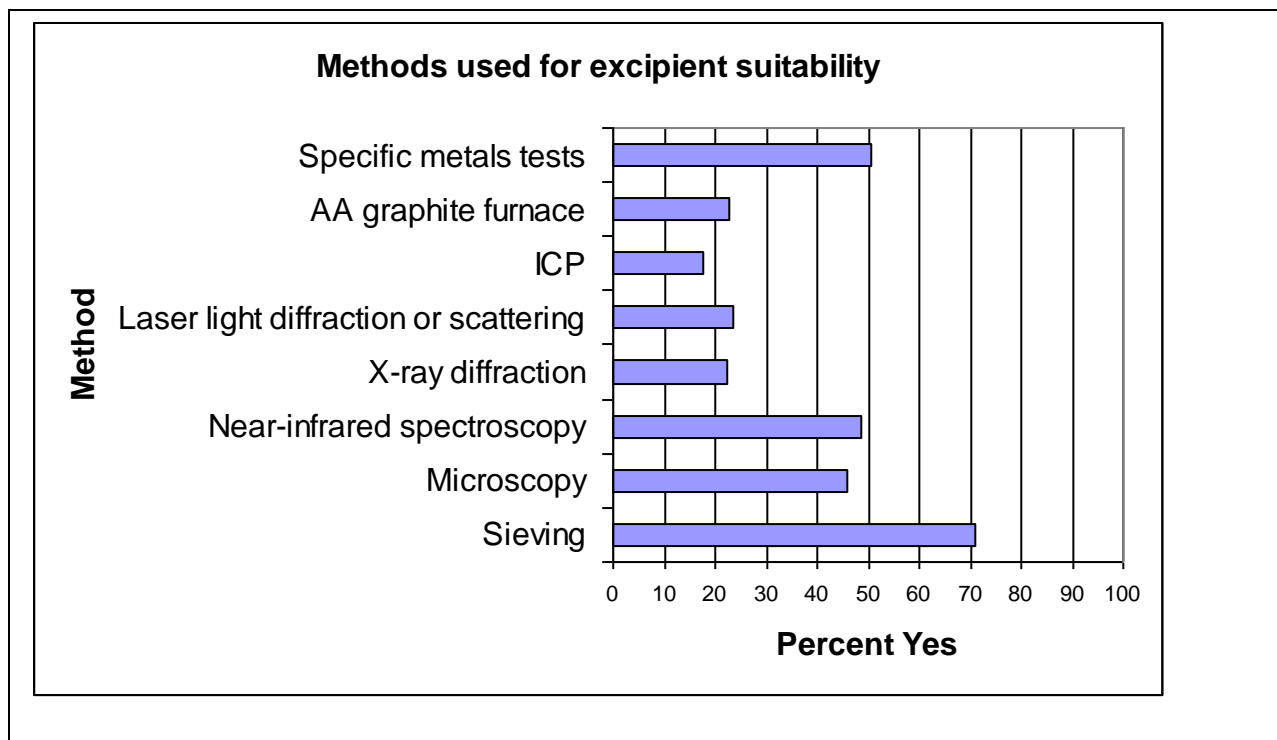


Figure 14: Methods for Suitability

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Drug product manufacturers’ conducting many additional tests indicates a need for compendial general chapters and information chapters that would guide the industry on excipient testing. The survey findings suggest that developing harmonized chapters by the three compendia for many tests noted above will help the drug product manufacturers in assessing and establishing the quality of excipients they purchase for use in the drug products.

MEETING GLOBAL REQUIREMENTS

Most excipient manufacturers (89%), excipient distributors (67%), and drug product manufacturers (90%) identified themselves as a multinational company, and the remaining to be a regional (operations in United States only) company. Information with respect to distribution and sale of their products within US, export, or both, is shown in Table 11.

Table 11: Respondent Product Distribution Profile

Supply Chain Function	Total # of responses	Distribution of products manufactured		
		Sold in US	Export only	Both
Excipient Manufacturer	26	2	1	23
Excipient Distributor	6	1	0	5
Drug Product Manufacturer	164	18	12	134
Totals	196	21	13	162

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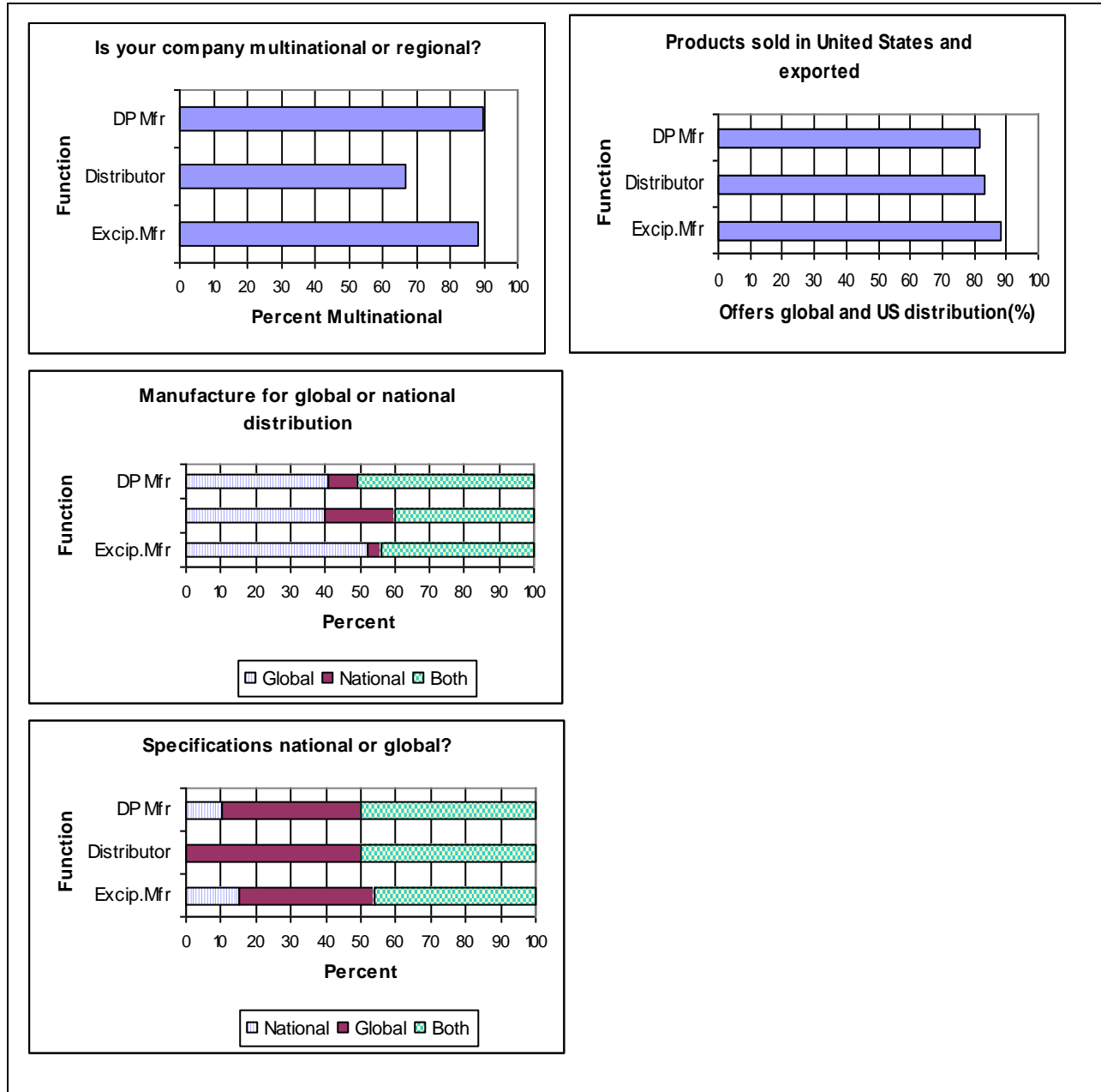
When a company is multinational, the products manufactured were sold within a country (or region), or globally, as shown in Table 12.

779
780

Table 12: Multinational Product Distribution

Supply Chain Function	Total # of responses	When a company is multinational, % of its products manufactured or distributed within		
		Different global regions	Its Nation, or region	Both
Excipient Manufacturer	25	52	4	44
Excipient Distributor	5	40	20	40
Drug Product Manufacturer	152	41	9	51

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Figure 15: Respondent Demographics

788 For all respondents, most excipient specifications are both national and global; and for just 10 to
789 15% of respondents in each supply chain, the specifications are “national” only. This indicates
790 the importance of compendial harmonization to the excipient manufacturer and the drug product
791 manufacturer.

792
793 Over half (55%) of excipient manufacturers and drug product manufacturers qualify excipient
794 test methods for an additional market (region, or global). Two thirds (67%) of excipient
795 manufacturers, and 57% drug product manufacturers validate their analytical procedures for
796 testing (some, most or all) excipients according to USP General Information Chapter <1225>, or
797 International Conference on Harmonisation of Technical Requirements for Registration of
798 Pharmaceuticals for Human Use (ICH) Q2A/Q2B Validation of Analytical Methods. When the
799 excipients are qualified for an additional market, 67% of excipients manufacturers, and 92% of
800 drug product manufacturers verify their excipient quality (for some, most or all excipients) by
801 complete testing by the compendial method. The quality of excipients is also verified by the
802 excipient manufacturer’s analytical method by 64% of excipient manufacturers and 44% drug
803 product manufacturers. This indicates that in-house methods are also used for testing the quality
804 of excipients.

805
806 When an excipient is qualified for an additional market, only 48% users accept an excipient from
807 a supplier based on C of A and with an identity test only (for some, most or all of the excipients).

808

809 **Use of alternate methods in testing of excipients**

810

811 The survey reported 50% or more of excipient manufacturers, distributors, and drug product
812 manufacturers test some, most or all of their excipients by alternate international (Ph.Eur., JP)
813 compendial methods instead of *USP-NF* (see Figure 7).

814

815 To confirm compliance for more than one compendium, 56% of excipient manufacturers and
816 65% of drug product manufacturers conduct complete testing to all required compendia for
817 some, most, or all of their excipients.

818

819 To confirm compliance with more than one compendium, only 41% (45 out of 110) of drug
820 product manufacturers approve material by conducting complete testing on an excipient
821 according to monograph requirement of one compendium, and accept C of A from supplier for
822 compliance with other compendia. To demonstrate compliance with more than one
823 compendium, 38% of drug product manufacturers perform identity test(s) when they receive a C
824 of A from the supplier indicating conformance to all required compendia.

825

826 To confirm compliance with more than one compendium, 87% of drug product manufacturers do
827 not accept an excipient based only on the C of A.

828

829 **Use of harmonized monographs**

830

831 Over half of excipient manufacturers (61%) and of drug product manufacturers (52%) conduct
832 testing per harmonized monograph, for some, most or all of their excipients.

833

834 Many excipient manufacturers (59%) and drug product manufacturers (58%) reduce redundant
 835 testing by evaluation of multiple compendial specifications (methods and acceptance criteria) for
 836 equivalence.

837
 838 Over half of excipient manufacturers (59%) and of drug product manufacturers (55%) reduce
 839 redundant testing by selecting the most stringent method or specification for confirming
 840 compliance with more than one compendium. About 53% (10 out of 19) of excipient
 841 manufacturers and 74% (91 out of 123) of drug product manufacturers stated that redundant
 842 testing could be reduced by at least 20%. Only two respondents indicated redundant testing
 843 would not be reduced.

844
 845 As more excipient and drug product manufacturers operate globally, the use of harmonized
 846 monographs will only grow. Presently, a majority of stakeholders use the most stringent test
 847 method, specification, or acceptance criteria for compliance, or may re-do testing for the same
 848 attribute using another pharmacopeial analytical procedure, resulting in redundant testing of the
 849 same attribute. As more harmonized monographs and general chapters become official, such a
 850 progress will help in reducing redundant testing.
 851

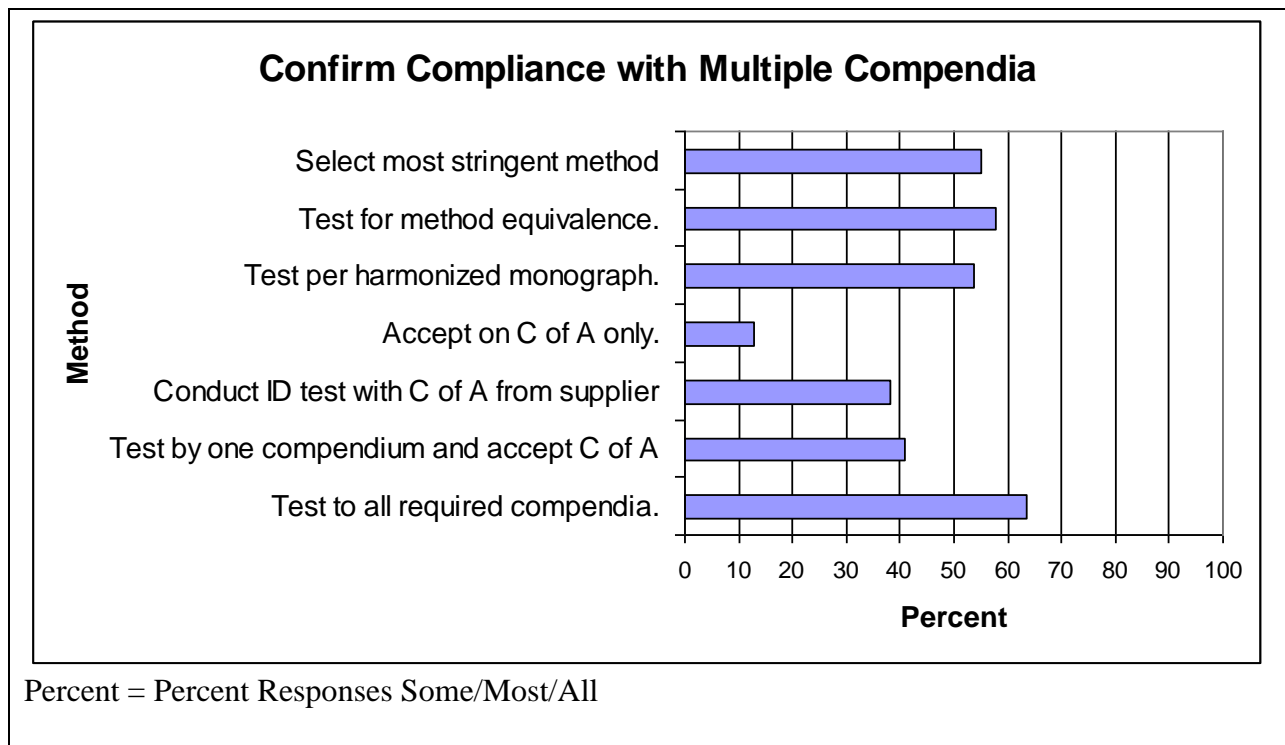


Figure 16: Compliance with Multiple Compendia

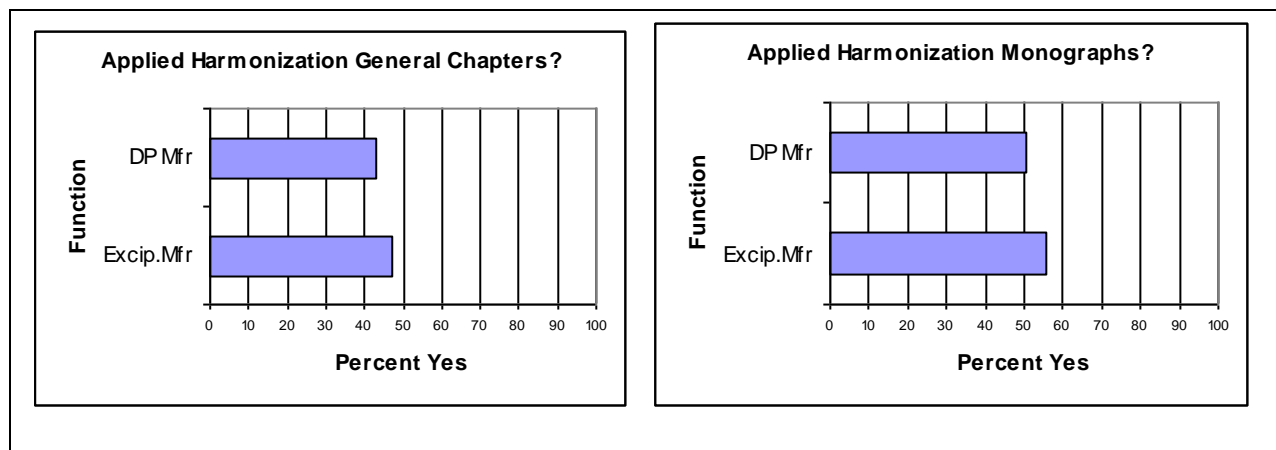
857 **PDG harmonization**

858
 859 Harmonized monographs have been applied across all of their sites by 56% of excipient
 860 manufacturers and 50% of drug product manufacturers.

861
 862 Three or more excipients are tested using harmonized monographs by 60% of excipient

863 manufacturers and 65% of drug product manufacturers.

864
865 Nearly half (8 out of 17) of excipient manufacturers and 43% (49 out of 114) drug product
866 manufacturers have applied harmonized general chapters across all sites. About 88% (7 out of 8)
867 excipient manufacturers and 72% drug product manufacturers use harmonized monographs
868 across all their sites.
869



870
871
872 **Figure 17: Compendial Harmonization**
873

874 The PDG harmonization effort by the three compendia has a great impact for the industry as
875 indicated by the data. This impact will only grow as more harmonized monographs and general
876 chapters are made official. Harmonization by PDG will benefit excipient manufacturer and users.
877

878 **SUMMARY OF KEY SURVEY FINDINGS**

879
880 The survey clearly indicates that majority of excipient manufacturers; excipient distributors and
881 drug product manufacturers manufacture their products for global distribution. They test their
882 excipients according to *USP-NF* monograph and general chapter methods. Almost all (97%) of
883 drug product manufacturers perform more than just the identification test when receiving
884 excipients from their vendors along with Certificate of Analysis.
885

886 New sources of excipients used by drug product manufacturers are qualified by vendor audits,
887 and complete testing of the excipient according to compendial monograph. Nearly half (40%) of
888 drug product manufacturers had difficulty in finding a manufacturer of *USP-NF* grade excipient.
889 In such a situation, they would use the best grade available, test the excipient according to
890 compendial monograph and conduct the excipient manufacturer's assessment. The majority
891 (75%) of drug product manufacturers indicated they ensure few to all excipients they use
892 conform to compendial grade by testing, along with manufacturer's site audits. In 80% of the
893 cases, validated test procedures are used to show a noncompendial grade excipient conforms to a
894 compendial grade, or a compendial grade conforms to a multi-compendia grade.
895

896 Majority of excipient manufacturers and distributors are not concerned about such factors as
897 GMP requirements being restrictive or low demand for compendial grade, or inability to meet
898 compendial monograph requirement, or potential to be inspected by FDA, or audits by drug

899 product manufacturers. Nearly 80% of excipient manufacturers, distributors and drug product
900 manufacturers have been inspected or visited by the FDA or State or local authorities. Almost
901 all (89%) of drug product manufacturers stated that at least 5 of their excipients are in the
902 reduced testing program, and do not perform complete monograph testing after vendor
903 qualification and receipt of Certificate of Analysis. Excipient manufacturers, distributors and
904 drug product manufacturers responded to be adequately familiar with the applicable FDA and
905 compendial requirements and recommendations related to testing of excipients used in a drug
906 product.

907
908 For *USP-NF* excipients, 70% or more excipient manufacturers, distributors, and drug product
909 manufacturers perform additional functionality or processability testing that is not part of any
910 (*USP-NF*, Ph.Eur., JP) compendial monograph, due to processing concerns (87%), and most of
911 them (87%) for solid oral dosage forms. One quarter (24%) of drug product manufacturers have
912 products for which excipient variability is a problem in spite of such extra-compendial testing.

913
914 Half or more of excipient manufacturers, distributors and drug product manufacturers test some,
915 most or all of their excipients by alternate international compendial methods instead of *USP-NF*.

916
917 Nearly 60% of excipient manufacturers and drug product manufacturers conduct excipient
918 testing per harmonized monographs; and reduce redundant testing by demonstrating multiple
919 compendial specification equivalence, or by using the most stringent method or specification for
920 confirming compliance with more than one compendium.

921
922 About 50% of excipient manufacturers and drug product manufacturers have applied harmonized
923 excipient monographs and harmonized general chapters across all their sites.

924

925 **EXCIPIENT WORKING GROUP RECOMMENDATIONS FOR DISCUSSION**

926

927 The PQRI Excipient Working Group recommends these topics be discussed at a workshop as
928 opportunities for regulatory improvement.⁷

929

930 1. Various approaches allowed by 21 CFR Part 211.84 regulations are not fully utilized by
931 the industry. Industry and FDA should dialog on successful implementation of excipient
932 control strategies, and ways to remove obstacles to using the various approaches to
933 comply with regulations, in order to increase efficiency.

934

935 2. Drug Product Manufacturers are performing many additional tests to characterize
936 excipient physical and chemical properties. Industry and *USP-NF* should work together
937 to update or create new General Information Chapters to characterize these excipient
938 properties.

939

⁷ PQRI workshop on Excipient Testing and Control Strategies has been scheduled for October 10th and 11th, 2006 at the Marriott Bethesda North Conference Center in Maryland.

- 940 3. Auditing of excipient manufacturers, distributors, and testing laboratories is not
941 performed by 3rd parties. Each drug product manufacturer uses their own auditors. Both
942 excipient manufacturers and drug product manufacturers may gain efficiency and
943 maintain regulatory compliance by use of reliable 3rd party audits.
944
- 945 4. Skip lot testing is a valuable tool for the industry. Clarification on the use of skip lot
946 testing for excipients is needed from the FDA. Process analytical technology (PAT)
947 when applied to “continuous flow” manufacturing and process qualification can justify
948 skip lot testing.
949
- 950 5. The labeling requirement for compendial excipients needs to be clarified. A number of
951 drug product manufacturers experience difficulties obtaining *USP-NF* labeled materials.
952 All stakeholders should work together to reverse the trend in the non-availability of
953 excipients formerly labeled as *USP-NF*, determine the correct approach(es) **for using** an
954 excipient not labeled *USP-NF*, and to determine the resulting changes needed in
955 regulatory submissions.
956
- 957 6. When former *USP-NF* labeled materials (excipients) become not available:
958
- 959 • *USP-NF* should retain the monograph as the drug manufacturer can indicate they test
960 per *USP-NF* in their regulatory filing, thereby eliminating method justification and
961 analytical method validation sections for the excipients.
 - 962 • Drug Master Files (DMFs) become less valuable, since DMFs are not FDA-reviewed
963 until referenced in an application with permission of the DMF holder.
 - 964 • The recent decision to no longer maintain the Food Chemical Codex complicates the
965 problem.
966
- 967 7. International compendial harmonization through Pharmacopoeial Discussion Group, use
968 of alternate methods, and reducing redundant testing are having a large positive impact
969 on the industry. Survey responses estimate 20 to 60% reduction in redundant testing
970 with compendial harmonization. This can lead to more efficiency for FDA and US
971 industry (excipient manufacturer and users.)
972