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

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

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

It is to be noted that “Subpart E – Control of Components and Drug Product Containers and Closures of Title 21 Code of Federal Regulations Part 211 – Current Good Manufacturing
Practice for Finished Pharmaceuticals” apply to sampling, testing, release, and use of excipients as drug product components. “21 CFR Part 211.84, Testing and approval or rejection of components, drug product containers and closures” describes the sampling, examination and testing, approval, and release of an excipient for use in the manufacturing of a drug product, by a drug product manufacturer. 21 CFR 211.84(d) requirements (1) & (2) are, “(1) At least one test shall be conducted to verify the identity of each component of a drug product. Specific identity tests, if they exist, shall be used.”; “(2) Each component shall be tested for conformity with all appropriate written specifications for purity, strength, and quality. In lieu of such testing by the manufacturer, a report of analysis may be accepted from the supplier of a component, provided that at least one specific identity test is conducted on such component by the (drug product) manufacturer, and provided that the (drug product) manufacturer establishes the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals.” Additional regulatory requirements that may also apply can be found at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=211&showFR=1&subpartNode=21:4.0.1.1.10.5 1. 

The USP—NF General Notices2, under Tests and Assays states that “Every compendial article in commerce shall be so constituted that when examined in accordance with these assay and test procedures, it meets all of the requirements in the monograph defining it. However, it is not to be inferred that application of every analytical procedure in the monograph to samples from every production batch is necessarily a prerequisite for assuring compliance with Pharmacopeial standards before the batch is released for distribution. Data derived from manufacturing process validation studies and from in-process controls may provide greater assurance that a batch meets a particular monograph requirement than analytical data derived from an examination of finished units drawn from that batch. On the basis of such assurances, the analytical procedures in the monograph may be omitted by the manufacturer in judging compliance of the batch with the Pharmacopeial standards.”

Survey Highlights

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

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

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

**Surprises**

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

**Tables**

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<th>13</th>
</tr>
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Background

When the European Agency for the Evaluation of Medicinal Products \(^3\) and US Food and Drug Administration \(^4\) issued excipients guidance in 2003, industry predicted that they would have the unintended result of causing additional paperwork and excessive testing for excipient control strategies, without adding benefits. In addition, industry believed the guidance effectively eliminated generally accepted and common excipient control strategies.

FDA interpretation of ICH CTD language used in sections P.4 Control of Excipients \(^4\) required that manufacturers specify each method used for routine testing of excipients, unless the method is exactly that of the pharmacopeia and full monograph testing is performed.

Often a drug-product manufacturer has methods used internally that are shown to produce equivalent results to those in a pharmacopeia. Also, many manufacturers with global markets seek to eliminate redundant testing of the same property by selecting a single method shown to be capable of ensuring compliance with requirements of many pharmacopeias. The United States Pharmacopeia has been clear that alternate methods are acceptable to demonstrate compliance with \textit{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)\(^6\), 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)
\(^{5}\) \textit{USP—NF} General Notices , section Tests and Assays under Procedures.
FDA recently announced its "Guidance for Industry on Chemistry, Manufacturing, and Controls Information; Withdrawal and Revision of Seven Guidances". By focusing on the Pharmaceutical Current Good Manufacturing Practices (CGMPs) for the 21st Century (CGMP Initiative) and ICH Guidelines, FDA has strategically reduced industry's regulatory and paperwork concerns, and changed the regulatory focus to concentrate on those aspects of manufacturing that pose the greatest risk to the quality of the product. Although excipients constitute a large portion of most drug products, they have been viewed as a low-risk aspect of drug-product safety. They are, however, a key aspect of product Quality by Design (QbD).

**Definitions**

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

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

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

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

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

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

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

A. Section 201(g)(1) of Federal FD&C Act, Definition of the term Drug.  
(http://www.fda.gov/opacom/laws/fdact/fdact1.htm. Scroll down to g(1) to see the definition of Drug.)

B. Part 211.84 of Title 21 CFR, Testing and approval or rejection of components, drug product containers, and closures.  
(http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfsearch.cfm and type 211.84 in the first search box to look at the regulations)

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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).
C. FDA’s Changes to an Approved NDA or ANDA Guidance, dated April 2004.

D. FDA’s Drug Product Guidance, Chapters II and III, Drug Products (NDAs and ANDAs) and Investigational Formulations (INDs), dated February 1987.
   (http://www.fda.gov/cder/guidance/old029fn.pdf)

   (http://www.fda.gov/cder/guidance/1215dft.pdf)

F. FDA’s “Guidance for Industry on Chemistry, Manufacturing, and Controls Information; Withdrawal and Revision of Seven Guidances," Federal Register 71(105), 31194-31195, dated June 1, 2006.


H. 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 USP-NF. (http://store.usp.org/)

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

RESPONSES FROM EXCIPIENT MANUFACTURERS, EXCIPIENT DISTRIBUTORS, AND DRUG PRODUCT MANUFACTURERS (EXCIPIENT USERS)

Demographics of survey respondents

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

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

Compliance with Pharmacopeial monograph requirements

Most excipient specifications are both national and global (USP-NF, Ph.Eur., JP), and 10-15% just national. Almost all (99%) respondents indicated that their excipient specifications comply with USP-NF, 92% comply with Ph.Eur., and 83% comply with JP.
A large majority, 97% of drug product manufacturers test their excipients according to USP-NF monograph/General Chapter methods. About 16% of excipient manufacturers and distributors do not test their products according to USP-NF monograph/General Chapter methods.

![Graphs showing compliance with compendial requirements](image)

**Figure 1: Compliance with Compendial Requirements**

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

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

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

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

When an excipient manufacturer has been audited, qualified, and has performed all tests according to compendia, or as approved in a drug product application, 49% of drug product manufacturers accept the material by performing ID test only (per 21 CFR 211.84) along with the manufacturer’s C of A. Almost all (97%) drug product manufacturers perform more than just
the ID test before accepting an excipient. This clearly indicates that drug product manufacturers perform more testing on excipients they receive from their suppliers than minimally required by US FDA regulations. This finding also demonstrates drug product manufacturers’ awareness and efforts to perform such additional testing towards successfully manufacturing their drug product batches.

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

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

![Bar charts showing responses to accepting excipients based on process controls or certificate of analysis.](image)

![Bar chart showing responses to testing excipient suitability using experimental or pilot scale.](image)

Figure 2: Verification of Excipient Quality
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.
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.
One out of six distributors, and 82% (75 out of 91) drug product manufacturers provided (or had) services for testing excipients according to compendia.

**Difficulty finding manufacturers of USP-NF grade excipients?**

<table>
<thead>
<tr>
<th>Function</th>
<th>Percent Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>DP Mfr</td>
<td></td>
</tr>
<tr>
<td>Distributor</td>
<td></td>
</tr>
</tbody>
</table>

**If yes, action is to:**

- Use another compendial grade material
- Contact FDA for direction
- Continue to use best grade available
- Reformulate product with another excipient
- Conduct vendor audit
- Test per USP-NF monograph

Percent = Percent Responses Some/Most/All

*Figure 4: Difficulty finding Manufacturer of USP-NF grade excipient*
Testing of a noncompendial grade excipient to conform to compendial grade by testing and manufacturing site audit

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

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

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

Conformance of a compendial excipient to multi-compendial grade by testing

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

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

Audit of excipient manufacturer and testing sites by Drug Product Manufacturers

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

While 25% of drug product manufacturers audit most or all of their excipient manufacturers through site visits, nearly 50% have visited their excipient distribution chain for some, most or
all of their excipients. About one-fourth (27%) of drug product manufacturers have not visited their excipient distribution chain for auditing.

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

![Have you audited?](chart)

**Figure 5: Excipient Audits**

**Frequency and method of auditing by Drug Product Manufacturers**

Frequency of audits performed by drug product manufacturers, of excipient manufacturer or supplier sites, excipient testing sites, excipient agents and excipient distribution chain are shown in Table 1.

Table 1: Drug Product Manufacturers Frequency of Audits

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

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

Methods used by drug product manufacturers for auditing the sites mentioned in Table 1 above are:
Table 2: Drug Product Manufacturers Audit Methods

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

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

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

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

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

More than 50% of excipient manufacturers, excipient distributors, and drug product manufacturers test excipients by alternate compendial methods including Ph.Eur. and JP.
TOPICS SPECIFIC TO EXCIPIENT MANUFACTURERS

Labeling of excipients as Compendial Grade

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

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

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

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

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

**Table 3: Excipient Manufacturer’s Decision to Label**

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

**Table 4: Distributor's Decision to Label**

<table>
<thead>
<tr>
<th>Distributor’s decision impacted by:</th>
<th>None</th>
<th>Few</th>
<th>Some</th>
<th>Most</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>GMP requirements are too restrictive</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Low demand for compendial grade</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Can’t meet the compendial monograph</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Potential to be inspected by FDA</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Internal time resources required for Pharmaceutical Manufacturer Audits</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>
Audit of Excipient Manufacturers by Drug Product Manufacturers

Out of 17 excipient manufacturers who responded, 9 stated that most of their customers have audited them, and 7 stated that some of their customers have audited them. Only one excipient manufacturer stated that all of their customers have audited them. Most (13 of 17) stated that their audits were by on-site visit of their “customer’s auditors” most of the time. Three excipient manufacturers were visited by ‘some’ of their customers, and only one excipient manufacturer stated that they were visited by ‘few’ of their customer’s auditors.
Third party audits and audits by questionnaire to excipient manufacturers by their customers are shown in Table 5.

<table>
<thead>
<tr>
<th>Method used for auditing of an excipient manufacturer</th>
<th># of respondents</th>
<th>None</th>
<th>Few</th>
<th>Some</th>
<th>Most</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Third Party Audit</td>
<td>14</td>
<td>4</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Customer’s Questionnaire</td>
<td>17</td>
<td>1</td>
<td>4</td>
<td>8</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

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

**Auditing of raw material suppliers by Excipient Manufacturers**

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

**Industry standards used by excipient manufacturers, and desired by distributors and drug product manufacturers**

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

The USP General Information Chapter <1078> is the most commonly used voluntary industry standard. Note that the original IPEC GMP is the basis of the USP-NF standard, and that a new Joint IPEC-PQG Guide was launched January 26, 2006. It is expected that USP-NF will update <1078> to align with the Joint IPEC-PQG Guide.
### Table 6: Industry Standards

<table>
<thead>
<tr>
<th>Recommended voluntary industry standards used or desired</th>
<th>Excipient Manufacturers</th>
<th>Excipient Distributors</th>
<th>Drug Product Manufacturers</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Note: Not all questions of the survey were answered by respondents)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total # of responses received</strong></td>
<td>14 to 17</td>
<td>4 to 5</td>
<td>78 to 101</td>
</tr>
<tr>
<td>International Pharmaceutical Excipients Council – Pharmaceutical Quality Group (IPEC-PQG) Guide</td>
<td>47%</td>
<td>53%</td>
<td>70%</td>
</tr>
<tr>
<td>IPEC Good Manufacturing Practices Guide for Bulk Pharmaceutical Excipients 2001</td>
<td>18%</td>
<td>82%</td>
<td>47%</td>
</tr>
<tr>
<td>USP &lt;1078&gt; Good Manufacturing Practices (GMPs) for Bulk Pharmaceutical Excipients</td>
<td>24%</td>
<td>76%</td>
<td>11%</td>
</tr>
<tr>
<td>World Health Organization (WHO); WHO expert committee on Specifications for Pharmaceutical Preparations, 35th Report, Geneva, WHO, 1999, Annex 5 (WHO Technical Series, No. 885; GMPs: Supplementary Guidelines for the manufacture of pharmaceutical excipients)</td>
<td>79%</td>
<td>21%</td>
<td>73%</td>
</tr>
</tbody>
</table>
TOPICS SPECIFIC TO EXCIPIENT DISTRIBUTORS

Excipient manufacturer assessment before distributing the product

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

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

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

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

Frequency and method of auditing by Distributors

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

Table 7: Audit Frequency by Distributors

<table>
<thead>
<tr>
<th>Excipient supply chain</th>
<th># of respondents</th>
<th>Never</th>
<th>Every year</th>
<th>Every 2 years</th>
<th>Every 3-4 years</th>
<th>Every 5+ years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer/supply site</td>
<td>4</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Testing site</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Agent</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Distribution chain</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

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

Table 8: Audit Methods by Distributors

<table>
<thead>
<tr>
<th>Method used for auditing</th>
<th># of respondents</th>
<th>None</th>
<th>Few</th>
<th>Some</th>
<th>Most</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onsite visit by Company auditors</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Third Party Audit</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Questionnaire</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Audit of Excipient Distributors by Drug Product Manufacturers

Out of the 4 distributors who responded, 2 stated that some of their customers have audited them, and the other 2 stated that most of their customers have audited them. One distributor stated that their audits were by on-site visit of their customer’s auditors all the time. Two distributors stated that drug product manufacturers audit them on-site most of the time, and one distributor stated that they have on-site audit by their customers, some of the time.
Third party audits and audits by questionnaire to the distributors, by their customers are shown in Table 9.

Table 9: Drug Product Manufacturer Audit Methods of Distributors

<table>
<thead>
<tr>
<th>Method used for auditing of a distributor by their customers</th>
<th># of respondents</th>
<th>None</th>
<th>Few</th>
<th>Some</th>
<th>Most</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onsite visit</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Third Party Audit</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Customer’s Questionnaire</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

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

INSPECTIONS BY FDA, STATE AND LOCAL AUTHORITIES

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

Most distributors (4 of 5) indicated that they have been inspected or visited by State or Local authorities.
Excipient control strategy questioned during routine GMP inspection

Figure 10: Inspections

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

<table>
<thead>
<tr>
<th>Applicable FDA and compendial requirements, and recommendations</th>
<th>Excipient Manufacturers</th>
<th>Excipient Distributors</th>
<th>Drug Product Manufacturers</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Note: Not all questions of the survey were answered by respondents)</td>
<td>No, or Some</td>
<td>Moderate, Very, or Complete</td>
<td>No, or Some</td>
</tr>
<tr>
<td><strong>Total # of responses received</strong></td>
<td>16 to 17</td>
<td>4</td>
<td>101 to 106</td>
</tr>
<tr>
<td>Section 201(g)(1) of the Federal FD&amp;C Act, Definition of the term Drug</td>
<td>18%</td>
<td>82%</td>
<td>25%</td>
</tr>
<tr>
<td>Title 21 CFR Part 211.84, Testing and approval or rejection of components, drug product containers and closures</td>
<td>24%</td>
<td>76%</td>
<td>25%</td>
</tr>
<tr>
<td>FDA’s Changes to an Approved NDA or ANDA Guidance, dated April 2004</td>
<td>53%</td>
<td>47%</td>
<td>25%</td>
</tr>
<tr>
<td>FDA’s Drug Product Guidance, Chapters II and III, Drug Products (NDAs and ANDAs) and Investigational Formulations (INDs), dated February 1987</td>
<td>59%</td>
<td>41%</td>
<td>25%</td>
</tr>
<tr>
<td>FDA’s Draft Guidance for Industry on Drug Product: Chemistry, Manufacturing and Controls Information, dated January 2003</td>
<td>47%</td>
<td>53%</td>
<td>0</td>
</tr>
<tr>
<td>Applicable FDA and compendial requirements, and recommendations</td>
<td>Excipient Manufacturers</td>
<td>Excipient Distributors</td>
<td>Drug Product Manufacturers</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
<td>-------------------------</td>
<td>------------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>(Note: Not all questions of the survey were answered by respondents)</td>
<td>No, or Some  Moderate, Very, or Complete</td>
<td>No, or Some  Moderate, Very, or Complete</td>
<td>No, or Some  Moderate, Very, or Complete</td>
</tr>
<tr>
<td>Total # of responses received</td>
<td>16 to 17</td>
<td>4</td>
<td>101 to 106</td>
</tr>
<tr>
<td>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</td>
<td>44%  56%</td>
<td>0  100%</td>
<td>27%  73%</td>
</tr>
<tr>
<td>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 <em>USP-NF</em></td>
<td>12%  88%</td>
<td>25%  75%</td>
<td>11%  89%</td>
</tr>
</tbody>
</table>
Figure 11: Familiarity with statutes, regulations, guidance and compendial requirements

Percent = Percent Responses Moderate/Very/Completely Familiar
USE OF REDUCED TESTING

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

---

**Figure 12: Vendor Certification**

<table>
<thead>
<tr>
<th>Question</th>
<th>Percent Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have a vendor certification program?</td>
<td>80%</td>
</tr>
<tr>
<td>Include C of A qualification?</td>
<td>90%</td>
</tr>
<tr>
<td>C of A means reduced testing?</td>
<td>85%</td>
</tr>
<tr>
<td>Reduced testing based on prior approval?</td>
<td>30%</td>
</tr>
</tbody>
</table>

---

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

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

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

For USP-NF excipients, 88% of excipient manufacturers (14 out of 16), 75% of distributors (3 out of 4), and 68% drug product manufacturers (75 out of 111) perform additional functionality or processability testing that is not part of any compendial monograph (USP-NF, Ph.Eur., JP). Over three-fourths (76%) of drug product manufacturer respondents perform such tests to determine excipient suitability for their intended use.
Most (12 out 15) excipient manufacturers perform such tests always for the excipient, and 20% of the time for one particular customer. Slightly fewer, (3 out of 5) distributors perform additional testing always for an excipient and 40% for one particular customer. About two thirds of drug product manufacturers (50 out of 78) perform additional testing always for an excipient, and 36% perform such additional testing, for one particular product.

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

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

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

Where the additional tests are performed

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

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

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

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

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

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

- 40% Sterility Tests
- 66% Bacterial Endotoxins Test
Laboratory methods used for performing extra-compendial tests are:

- 51% Specific metals tests
- 23% AA graphite furnace
- 17% ICP
- 23% Laser light diffraction or scattering
- 22% X-ray diffraction
- 49% Near Infrared Spectroscopy
- 46% Microscopy
- 71% Sieving

Figure 13: Tests for Suitability
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.

<p>| Table 11: Respondent Product Distribution Profile | Distribution of products manufactured |</p>
<table>
<thead>
<tr>
<th>Supply Chain Function</th>
<th>Total # of responses</th>
<th>Sold in US</th>
<th>Export only</th>
<th>Both</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excipient Manufacturer</td>
<td>26</td>
<td>2</td>
<td>1</td>
<td>23</td>
</tr>
<tr>
<td>Excipient Distributor</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Drug Product Manufacturer</td>
<td>164</td>
<td>18</td>
<td>12</td>
<td>134</td>
</tr>
<tr>
<td>Totals</td>
<td>196</td>
<td>21</td>
<td>13</td>
<td>162</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Supply Chain Function</th>
<th>Total # of responses</th>
<th>Different global regions</th>
<th>Its Nation, or region</th>
<th>Both</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excipient Manufacturer</td>
<td>25</td>
<td>52</td>
<td>4</td>
<td>44</td>
</tr>
<tr>
<td>Excipient Distributor</td>
<td>5</td>
<td>40</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>Drug Product Manufacturer</td>
<td>152</td>
<td>41</td>
<td>9</td>
<td>51</td>
</tr>
</tbody>
</table>

When a company is multinational, % of its products manufactured or distributed within

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

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

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

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

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

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

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

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

**Use of harmonized monographs**

Over half of excipient manufacturers (61%) and of drug product manufacturers (52%) conduct
testing per harmonized monograph, for some, most or all of their excipients.
Many excipient manufacturers (59%) and drug product manufacturers (58%) reduce redundant testing by evaluation of multiple compendial specifications (methods and acceptance criteria) for equivalence.

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

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

**Confirm Compliance with Multiple Compendia**

<table>
<thead>
<tr>
<th>Method</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Select most stringent method</td>
<td>60%</td>
</tr>
<tr>
<td>Test for method equivalence.</td>
<td>55%</td>
</tr>
<tr>
<td>Test per harmonized monograph.</td>
<td>50%</td>
</tr>
<tr>
<td>Accept on C of A only.</td>
<td>45%</td>
</tr>
<tr>
<td>Conduct ID test with C of A from supplier</td>
<td>40%</td>
</tr>
<tr>
<td>Test by one compendium and accept C of A</td>
<td>35%</td>
</tr>
<tr>
<td>Test to all required compendia.</td>
<td>30%</td>
</tr>
</tbody>
</table>

Percent = Percent Responses Some/Most/All

**Figure 16: Compliance with Multiple Compendia**

**PDG harmonization**

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

Three or more excipients are tested using harmonized monographs by 60% of excipient...
manufacturers and 65% of drug product manufacturers.

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

**Figure 17: Compendial Harmonization**

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

**SUMMARY OF KEY SURVEY FINDINGS**

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

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

Majority of excipient manufacturers and distributors are not concerned about such factors as GMP requirements being restrictive or low demand for compendial grade, or inability to meet compendial monograph requirement, or potential to be inspected by FDA, or audits by drug
product manufacturers. Nearly 80% of excipient manufacturers, distributors and drug product manufacturers have been inspected or visited by the FDA or State or local authorities. Almost all (89%) of drug product manufacturers stated that at least 5 of their excipients are in the reduced testing program, and do not perform complete monograph testing after vendor qualification and receipt of Certificate of Analysis. Excipient manufacturers, distributors and drug product manufacturers responded to be adequately familiar with the applicable FDA and compendial requirements and recommendations related to testing of excipients used in a drug product.

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

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

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

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

**EXCIPIENT WORKING GROUP RECOMMENDATIONS FOR DISCUSSION**

The PQRI Excipient Working Group recommends these topics be discussed at a workshop as opportunities for regulatory improvement.\(^7\)

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

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

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\(^7\) 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.
3. Auditing of excipient manufacturers, distributors, and testing laboratories is not performed by 3rd parties. Each drug product manufacturer uses their own auditors. Both excipient manufacturers and drug product manufacturers may gain efficiency and maintain regulatory compliance by use of reliable 3rd party audits.

4. Skip lot testing is a valuable tool for the industry. Clarification on the use of skip lot testing for excipients is needed from the FDA. Process analytical technology (PAT) when applied to “continuous flow” manufacturing and process qualification can justify skip lot testing.

5. The labeling requirement for compendial excipients needs to be clarified. A number of drug product manufacturers experience difficulties obtaining USP-NF labeled materials. All stakeholders should work together to reverse the trend in the non-availability of excipients formerly labeled as USP-NF, determine the correct approach(es) for using an excipient not labeled USP-NF, and to determine the resulting changes needed in regulatory submissions.

6. When former USP-NF labeled materials (excipients) become not available:
   - USP-NF should retain the monograph as the drug manufacturer can indicate they test per USP-NF in their regulatory filing, thereby eliminating method justification and analytical method validation sections for the excipients.
   - Drug Master Files (DMFs) become less valuable, since DMFs are not FDA-reviewed until referenced in an application with permission of the DMF holder.
   - The recent decision to no longer maintain the Food Chemical Codex complicates the problem.

7. International compendial harmonization through Pharmacopoeial Discussion Group, use of alternate methods, and reducing redundant testing are having a large positive impact on the industry. Survey responses estimate 20 to 60% reduction in redundant testing with compendial harmonization. This can lead to more efficiency for FDA and US industry (excipient manufacturer and users.)