Report on the Industry Blend Uniformity Practices Survey

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The Blend Uniformity Working Group was formed by PQRI to assess issues surrounding blend uniformity testing. As part of this work, the group conducted a survey of pharmaceutical manufacturers to gather information about current industry practices. This article presents the survey design, results, and a discussion of the findings.

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The Product Quality Research Initiative (PQRI, www.pqri.org) is a consortium of industry, academia, and regulators formed to address the gap between scientific knowledge and regulatory policy. One of PQRI's first initiatives was to form a Blend Uniformity Working Group (BUWG) to examine issues surrounding blend uniformity testing. As part of its work, the BUWG conducted a survey to assess general practices being used by solid dosage form manufacturers to assess blend uniformity. The survey was conducted in a blinded manner so that the identity of respondents was unknown.

The survey was mailed to 134 individuals whose names were culled from association and trade group records. Because the survey responses were blinded, only one individual was identified for each company. A list of all sponsors who currently have at least one solid oral dosage form approved was compiled from FDA's *Orange Book*. No contact information could be found for approximately 30 of these sponsors.

Of the 134 surveys distributed, 26 replies were received, and two replies containing surveys from two independent manufacturing sites also were received, giving a total of 28 responses. This represents a response rate of 20%, which was somewhat disappointing given the amount of attention the issue of blend uniformity testing has attracted from industry.

Survey design

The survey consisted of 22 questions and a space for general comments. Some definitions were provided in the instructions that accompanied the survey, and the reader is directed to the survey to find these definitions. The original survey with answers received can be found at www.pqri.org.

Demographics. Questions 1–6 profiled the type of respondent by soliciting information regarding the number of products being manufactured, whether blend uniformity (BU) testing was conducted during validation and/or on routine production batches, and how many products were currently subject to routine BU testing. This section also asked whether routine BU testing had been discontinued and how long it had been in place before being discontinued.

Testing methodology. Questions 7–9 sought information about the mechanics of blend sampling, including what device(s) are used, who takes blend samples, and the size of these samples.

Routine-batch testing. Questions 10–12 addressed BU testing for routine production batches. Question 10 asked about acceptance criteria, question 11 about the number of positional samples taken, and question 12 about the frequency of problems encountered.

Validation-batch testing. Questions 13–15 repeated questions 10–12 but specifically

According to survey results, a sample thief with side compartments is the most popular tool for use in blend uniformity testing.

Figure 1: Profile of respondents by number of solid oral dose products manufactured.

Figure 2: Number of products undergoing routine blend uniformity testing.

for BU testing on validation batches.

Failure. Question 16 asked respondents to indicate the most common cause of BU failure. Question 17 asked about the most common corrective action respondents had taken.

Cost. Questions 18 and 19 sought information about the cost of BU testing for routine production batches and for validation batches, respectively.

New technology. Questions 20 and 21 asked whether new technology had been used to assess BU. If new technology had not been used, respondents were asked to indicate why not.

Final comments. Question 22 asked whether the respondent would be prepared to provide blend uniformity and content uniformity data to the BUWG for the purpose of research. Question 23 provided a space for comments.

Results

Demographics. Of 28 respondents, 12 indicated that their firm manufactures >50 solid oral dosage products; 6 said their company had 25–50 solid oral products; 5 said 10–25; and 5 said <10 (see Figure 1). Given that the majority of companies are smaller manufacturers (as shown by the *Orange Book* survey), these survey results are somewhat biased in favor of larger manufacturers.

Of these firms, 18 said they perform BU testing on routine production batches. When asked to indicate the number of products that currently undergo or have undergone routine BU testing, 7 companies replied <5, 1 said 5–10, 6 said 11–20, and 4 said >20 products (see Figure 2). The slight majority of respondents who perform BU testing on routine production batches are doing so on 10 or more products, indicating a high level of experience in the BU testing of routine production batches among the respondents.

When survey participants were asked whether they had ever discontinued BU testing on routine production, 11 said no, 6 said yes via a supplement, and 1 responded yes without a supplement. Given the large number of products undergoing routine testing, the high proportion of respondents indicating that they had never

discontinued routine testing for any product is surprising.

When participants were asked how much experience is needed before discontinuing routine testing, the most common answer was 10–20 batches. No respondent felt that less than 10 batches was sufficient.

Testing methodology. When respondents were asked to indicate their primary sampling device, a thief with one side compartment and a thief with multiple side compartments were the clear favorites with 12 and 13 responses, respectively (see photo). This result means that the side-compartment thief design is the primary sampling device of 89.3% of respondents (25 out of 28 responses). The preference of secondary devices was evenly spread, although the bottom-plug thief was least favored — it gained only 3 responses between both primary and secondary device choices. Three respondents indicated that they take bulk samples and subsample as an alternative, 2 indicated that they use specialized sampling devices, and 1 indicated that samples are taken during discharge.

The most common answer to the question regarding the sample size taken for BU testing was no surprise: Twenty-one indicated 1–3 unit weights and 6 responded approximately one unit weight. Alternate sample sizes were fairly evenly spread among the options offered.

Routine-batch testing. Question 10 was a multipart question that addressed acceptance criteria for BU testing on routine production batches. Eighteen companies responded to this question. The most common percent relative standard deviation (%RSD) criterion was 4.1–5.9% (12 responses). Only 4 respondents indicated that requirements other than the most common existed, and only 1 indicated that they have no %RSD requirement.

The most common requirement for the mean of samples tested was 90–110% of label claim (14 responses). Only 7 indicated that they had another requirement for the mean. A significant number (6) indicated that 95–105% is the most common or other criterion for the mean.

The most common requirement for individual samples was 85–115% of label claim (9 respondents). The second most common was no requirement (6 respondents), followed by 90–110% of label claim (2 respondents), and 90–110% of the mean (1 respondent).

Finally, in Question 10, respondents were asked about their firm's policy on BU testing data treatment aside from the %RSD, mean, and individual results. When asked "Do you allow any form of

statistically based data treatment," 13 respondents said no. Respondents were equally divided on the allowance of both second-tier testing and superceding BU testing results with 9 answering yes to both of these options.

When survey participants were asked to indicate the number of positional samples taken from routine production batches, 14 respondents said 10 or less, 3 said 11–20, and 1 replied more than 20 (see Figure 3).

The final question in this section dealt with routine production-batch BU testing. Survey participants were asked to indicate the percentage of products (for which routine testing is conducted) that are problematic. The most common answer (11 responses) was 10% or less, followed by 4 respondents saying they have no problems, and 3 indicating that 10–25% of products are problematic (see Figure 4).

Validation-batch testing. The next section of the survey, Questions 13–15, repeated Questions 10–12 but were directed specifically to practices in validation-batch BU testing. Responses to questions regarding the requirements for %RSD, mean, and individuals were similar to those reported for routine-production batch testing, although more participants (28) responded to questions about validation batches.

Similar to the responses to the questions regarding routine-batch BU testing (Questions 10–12), the most common (22 responses) %RSD acceptance criteria for validation-batch BU testing was 4.1–5.9%, and the most common (15 responses) requirement for the mean was 90–110% of label claim. However, for the testing of validation batches, 7 respondents — one-fourth of the total number of respondents — indicated "no requirement" for the acceptance criteria for the mean of all samples, compared with no responses to this question for the testing of routine production batches. The most common (12 responses) acceptance criteria requirement for individuals was 85–115% of label claim. Relatively few respondents indicated the existence of acceptance requirements other than the most common.

The final section of Question 13 dealt with alternative data treatment. Survey participants were asked the following: "Do you utilize any form of statistical-based acceptance criteria (such as statistical process control, analysis by synthesis, standard deviation prediction interval, or Bergum's criteria)?" To this question, 20 out of 28 participants responded no (sim-
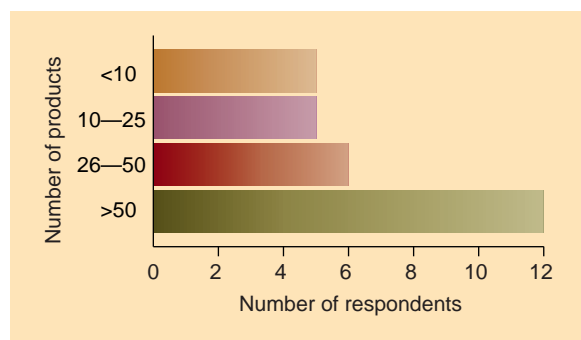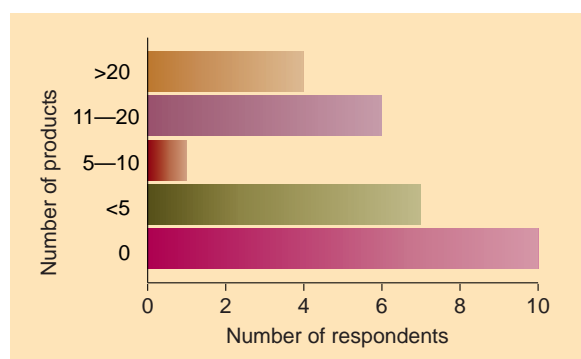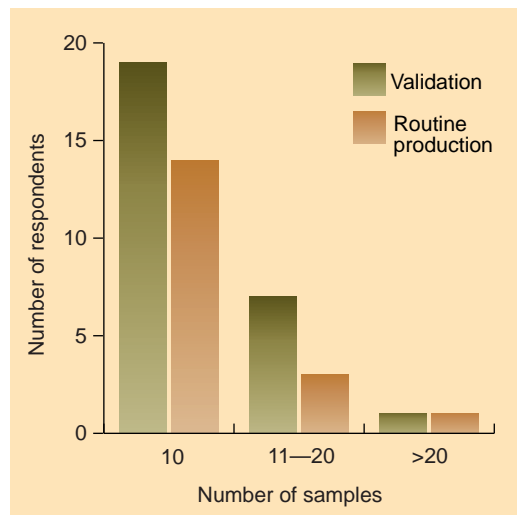
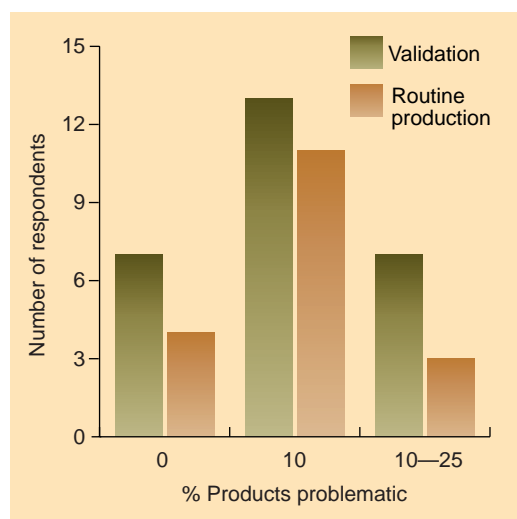**Figure 3:** Number of blend positional samples taken.

Figure 4: Proportion of products with problems in blend uniformity testing.
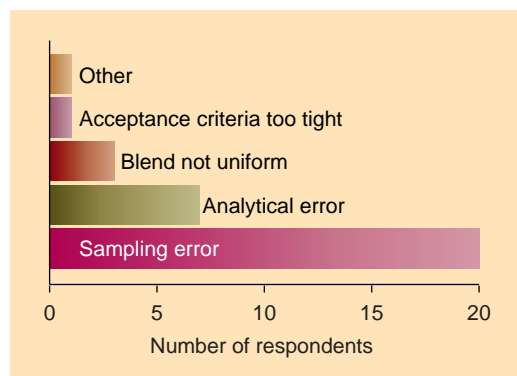

Figure 5: Most common cause of unsatisfactory blend uniformity testing.

ilar to the result for routine-batch testing in which 13 out of 18 replied no to this question). The following question inquired whether any form of second-tier testing was allowed in validation-batch BU testing, to which 15 respondents indicated yes. The final part of this question asked whether BU testing results for validation batches could be superceded with product (content uniformity) results or other forms of testing. A majority (18 out of 28) said no, whereas for the BU testing of routine batches only 9 out of 18 said no. This result suggests that there is more reluctance to supercede results during validation.

When survey participants were asked to indicate the number of positional samples taken for validation batches, 19 respondents answered 10 or less, and 7 answered 11–20. This result is surprising and indicates either little or no expansion of positional testing during validation or possibly indicates widespread use of bin blenders among respondents in which obtaining positional samples from much of the blender is not possible (see Figure 3).

Finally, when asked to indicate the number of products that were problematic during validation BU testing, 13 respondents said less than 10%, 7 reported no problems, and 7 responded 10–25%, similar to the responses to this question regarding routine production batch BU testing (see Figure 4).

Failure. Question 16 asked survey participants to indicate the most common cause of BU testing failure. As expected, 20 respondents said sampling error, followed by 7 saying analytical error. Perhaps somewhat surprising is that only 3 thought it is because the blend is not uniform (see Figure 5).

Survey participants were asked to indicate the most common action taken after a BU testing failure on one or more batches. To this question, 13 respondents said they perform extended content uniformity testing of finished dosage units, 7 choose to repeat sampling and testing, and 6 said they conduct extended blend sampling and testing. Five respondents indicated "other" to this question, which generally represents that more than one of the suggested actions is taken.

Cost. The cost of performing BU testing on routine production batches was es-

timated to be $501–1000 per batch by 11 respondents, $1001–2000 per batch by 6 respondents, and more than $2000 per batch by 5 respondents.

Question 19 asked participants to indicate the highest cost encountered and an estimated average cost of performing BU testing during validation, including the cost of lost batches. The question intended these costs to cover the whole validation exercise, however, as indicated by some responses, this question may have been been interpreted as referring to the cost per batch. Answers were very diverse ranging from more than $1 million as the highest cost to $3000. Average cost was also diverse, with most indicating $2000–3000, although two respondents gave much higher estimates between approximately $100,000 and $200,000.

New technology. The use of novel technology to assess blend uniformity does not appear to be significant. Twenty-six out of 28 respondents answered that they had not used any novel methods.

The most common reason participants gave for not using novel technology was concern about regulatory acceptance (11 responses), followed by "too costly to implement" (8 responses), and "do not have problems with current technology" (5 responses).

Final comments. Finally, when asked whether respondents would be prepared to provide blend uniformity and content uniformity data to the BUWG to enable research on results obtained, 19 indicated they would be willing to do this.

Nine respondents provided written comments. The majority of these questioned the need to perform routine testing or complained that there is no way of discontinuing this testing at present. Other comments included the fact that blend testing does not take into account post-blending powder handling and that apparently failed BU testing leads to the unnecessary loss of good batches. One comment urged the BUWG to work closely with FDA during the process of seeking remedies for BU testing problems.

Discussion

Overall, this survey's results provided few surprises concerning current industry practices surrounding BU testing. The relatively low response rate of 20% and the bias toward larger manufacturers should be borne in mind when interpreting the results.

There seems to be considerable experience among firms who are conducting BU testing on routine production batches, with the majority performing this testing

on 10 or more products. The relatively low rate of discontinuance of routine testing was surprising given that most respondents felt that 10–20 routine production batches would provide sufficient assurance to warrant discontinuation of BU testing.

The overwhelming majority use sampling thieves with either single or multiple side volumetric compartments, so-called grain thieves. Secondary sampling devices were fairly evenly spread among alternative designs, although the bottom-plug thief was by far the least used. This would indicate that firms are conservative in their choice of sampling devices, perhaps preferring to stay with the sampling device that they know best. It also indicates that no alternative design has gained significant acceptance among manufacturers. Similarly, the most common blend sample sizes are 1–3 unit weight or one unit weight. This is to be expected because approximately one unit weight has been suggested by FDA and the Barr Decision introduced the notion of 1–3 unit weights for low-weight dosage forms. Apparently, taking larger sample sizes is either not seen as acceptable or may offer no advantage, although many respondents indicated that larger sample sizes are used on occasion.

Acceptance criteria most commonly used were in line with current draft guidance for routine production batches. Most respondents indicated that the mean requirement is 90–110% of label claim with a %RSD requirement between 4.1% and 5.9%. This encompasses the draft guidance requirements. Requirements for individuals are 85–115% for half the respondents, followed by no requirement. The current draft guidance has no requirement for individuals, so the 85–115% may represent abbreviated new drug applications approved before the draft guidance. The majority of respondents indicated that they take 10 or fewer positional samples, which would be in agreement with the draft guidance.

The issue of alternative treatments of BU testing data showed that very few respondents applied statistical data treatment procedures. However, respondents were evenly split on whether they allow second-tier testing or whether they can override BU testing with other data such as expanded content uniformity testing. Finally, most respondents indicated that 10% or less of products subject to routine production batch testing are problematic.

The answers to these questions for validation batches only produced a few areas of difference. The most common requirement for %RSD remained 4.1–5.9%

and 90–110% for the mean, although a significant group have no requirement for the mean; whereas for routine batches, no respondent indicated no requirement for the mean. The most common requirement for individuals remained 85–115%, although 21.4% of respondents indicated 90–110% versus 11.1% of respondents for routine production batches. Answers for alternative treatments were similar except that slightly more respondents indicated that they would not override BU testing data for validation batches (66.7% versus 50% of respondents). The most unexpected answer is that 70.4% of respondents indicated they take 10 or fewer positional samples for validation batches, meaning very few firms extend positional sampling for validation batches. The percentage of problematic products remains unchanged for validation and routine batches, suggesting that if problems occur they are apparent at the start of commercial manufacture.

The most common causes of BU testing failure were sampling error and analytical error, with only a small number of respondents indicating "blend not uniform." As expected, this indicates blend uniformity testing procedures as the cause of failures rather than the blend itself.

Responses to the most common action following failure centered on finished dosage form testing or some form of blend retesting, which is in line with perceived causes of failure. Few respondents use remixing of the blend or variancing the batch to waste.

The cost of routine BU testing most commonly estimated was between $501 and $2000 per batch, which is in line with estimates made by the BUWG. Only 21.7% of respondents estimated more than $2000 per batch. The estimates made for the cost of validation exercises varied greatly. It is thought that this question, which was intended to solicit the overall cost for validation, may have been misin-

terpreted by some respondents as a per-batch cost. The information obtained is therefore of somewhat dubious value. The responses varied widely among respondents; however, few indicated that the cost was significantly different from routine production batches.

New technology for BU testing is clearly not currently favored with an overwhelming 92.9% of respondents saying they had not used new technology. Responses as to why not were (in order from most common to least) concern about regulatory acceptance, too costly to implement, and no problems with current technology. Clearly novel technology for BU testing has not gained acceptance at this time.

There were written comments from 9 of the 28 surveys returned, with the majority questioning the need for or value of performing BU testing on routine production batches.

Conclusion

The picture that emerges from the results of this survey is of a very conservative group that conducts BU testing with old physical sampling devices, taking 1–3 dosage unit samples, and conventional analytical methodology and testing to generally accepted criteria. Almost all report having trouble with a minority of products, about 10%, and this trouble seems apparent right from validation. The primary causes of failure are ascribed to sampling error and analytical error. The majority of respondents are prepared to overcome BU testing failure with either additional blend sampling and/or testing or with extended content uniformity or a combination thereof. This is in line with the expressed belief that the causes of failure are the sampling and testing procedures and not the blend itself. **PT**