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Report

Report on the PQRI Impurity Characterization and Quantification Best Practices Survey

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INTRODUCTION

The Product Quality Research Institute (PQRI, http://www.pqri.org) is a consortium of industry, academia, the Food and Drug Administration (FDA), and the United States Pharmacopeia (USP) that was formed to conduct research to generate scientific information to support regulatory policy. PQRI research will identify and address potential gaps between scientific knowledge and regulatory policy to reduce regulatory burden.

One of the working groups established under the PQRI's Drug Substance Technical Committee is the Impurity Working Group (IWG). The IWG project approved by the PQRI Steering Committee was to determine if too much effort is being devoted to the evaluation of impurities during early stages of drug development. If unnecessary resources were devoted at the early stages of drug development, then the next step would be to make specific recommendations with one possible outcome being the establishment of an FDA guidance that would specifically address what is required for evaluating impurities at the early stages of drug development. Therefore, a survey was developed to determine the current practices in the industry with respect to structure elucidation, quantification, and regulatory considerations prior to agency submission. The survey was conducted in a blinded manner so that the identity of the respondents was unknown.

The survey was mailed to 90 individuals who had been previously contacted to determine if they were the correct individuals in the organization to receive the survey and to encourage their participation. The original names were taken from association and trade group records. Additional surveys were distributed at the Annual American Association of Pharmaceutical Scientists (AAPS) meeting in November 2002 and the Impurity and Leachables meeting sponsored by the Institute for International Research in December 2002. Twenty-five responses were received and the analysis in this report was derived from the data of these responses. The PQRI IWG data review was finalized in June 2003. A preliminary report was presented at the PQRI workshop, "Good Regulation Through Good Science" in August 2003. The full survey report was drafted in January 2004 and sent to the PQRI Drug Substance Technical Committee in February 2004 for review. The IWG revised draft was sent to the technical, steering, and educational committees for review from July 2004 to September 2004. The manuscript was forwarded to *Pharmaceutical Research* in November 2004 for review. The survey summary does not make specific regulatory recommendations but seeks to report the survey results.

SURVEY DESIGN

The survey consisted of 25 questions that were divided into four sections. 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 can be found at http://www.pqri.org.

SECTION 1: STRUCTURAL CHARACTERIZATION/ ELUCIDATION OF IMPURITIES

Questions 1–8 sought information about the types of methodologies used at the various stages of drug development (prephase 1, phase 1, phase 2, and phase 3), the level of impurities that triggers structural elucidation, and the opinion of the respondent for the need for guidance on the subject.

SECTION 2: QUANTIFICATION

Questions 9–19 sought information regarding the types of methods used for quantification, the use of reference standards, the level of validation, and what approaches were used for ensuring all impurities were determined.

SECTION 3: REGULATORY

Questions 20–22 sought information to determine if current practice was based on scientific need or a perceived

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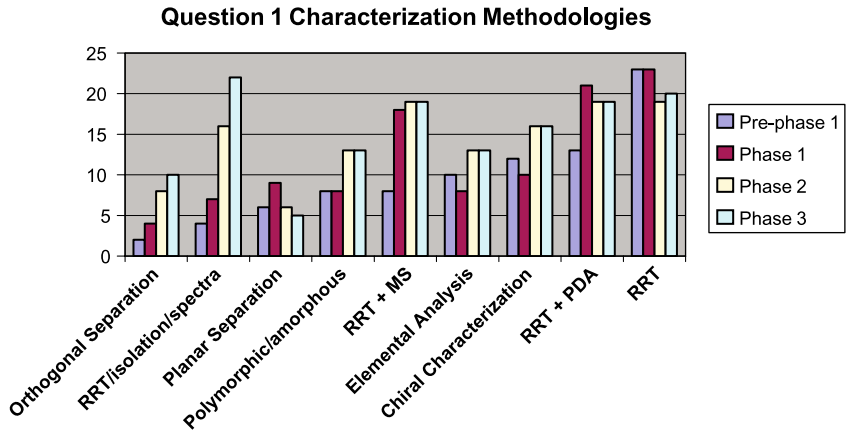

Fig. 1. Types of methods used by respondents in each phase.

regulatory requirement and if further guidance was required on the overall topic.

SECTION 4: DEMOGRAPHICS

Questions 23–25 profiled the type of respondent by asking information regarding the number of products being manufactured, the department of the respondent, and the size of the department.

RESULTS

Structural Characterization/Elucidation of Impurities

The response to Question 1, "What *typical* impurity characterization methodologies [check all that apply] are implemented in prephase 1, phase 1, phase 2, phase 3," is summarized in Fig. 1.

The responses support the following: In prephase 1, nearly all respondents used relative retention time (RRT), whereas many also used photodiode array (PDA) detection. In phase 1, nearly all used RRT, whereas many also used PDA and liquid chromatography–mass spectrometry (LC–MS). In phase 2, many also isolated impurities. In phase 3, more, but not all, isolated impurities.

Overall, the trend is from RRT in prephase 1 to isolation and structural analysis in phase 3. Listed in Fig. 2 is the actual average number of techniques used per phase for question 1.

Question 2 asked whether the respondent felt there was a need to harmonize the methodologies for each phase of drug development; 52% responded yes and 44% responded no. Most of the larger companies did not believe the need to harmonize methodologies, whereas smaller companies supported a harmonization approach. It should be noted that not all respondents answered this question and the data in Fig. 3 reflect a total of 21 responses (Level: See demographics).

Question 2a asked what are the minimum criteria for impurity characterization methodologies at each phase of drug development.

At prephase 1, 56% felt that RTT was the minimum criterion needed. At phase 1, 60% felt RRT was sufficient, 44% felt MS was sufficient, and 24% felt UV spectroscopy (UV) was sufficient. At phase 2, 40% responded MS was sufficient and 8% felt full identification was necessary. At phase 3, 48% responded that full isolation and identification were required. The trend for the minimum criteria for impurity characterization is from RRT in prephase 1 to full isolation and characterization in phase 3.

Question 3 asked what impurity threshold level triggered structural elucidation (assuming a daily dose of less than 2 g) at each of the drug development phases (Fig. 4).

None of the respondents indicated they did structural elucidation when the level of the impurity was less than 0.05%. Most respondents indicated 0.25 to 0.5% at prephase 1; 0.1 to less than 0.25% at phase 1; and 0.1% at phase 2, phase 3, and at new drug application (NDA)/abbreviated new drug application (ANDA). However, 44% indicated that at NDA/ANDA the level is 0.25% to greater than 0.5%. Figure 5 shows the trend for the trigger level at each phase. The International Conference on Harmonization (ICH) Guidance for Impurities requires impurity characterization at 0.1%

Question 4 asked if degradation products were treated the same as impurities with respect to the threshold for structure elucidation. Eighty percent of the respondents treated degradation products the same as impurities for setting the threshold for structural elucidation.

Question 5 asked if purposeful degradation studies were performed. All respondents (100%) did purposeful degradation studies to aid in the characterization of impurities.

Question 6 asked what are the practices in terms of conditions used to degrade sample. Ninety-two percent used various conditions of acid, base, oxidation, and light, whereas 56% used heat only.

Question 7 asked what is an acceptable range for mass balance for purposeful degradation studies. Thirty-six percent

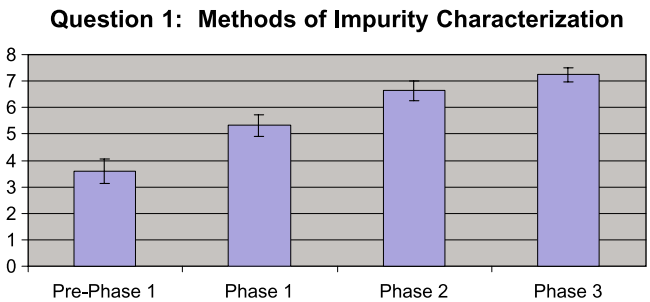

Fig. 2. Average number of methods used by respondents in each phase.

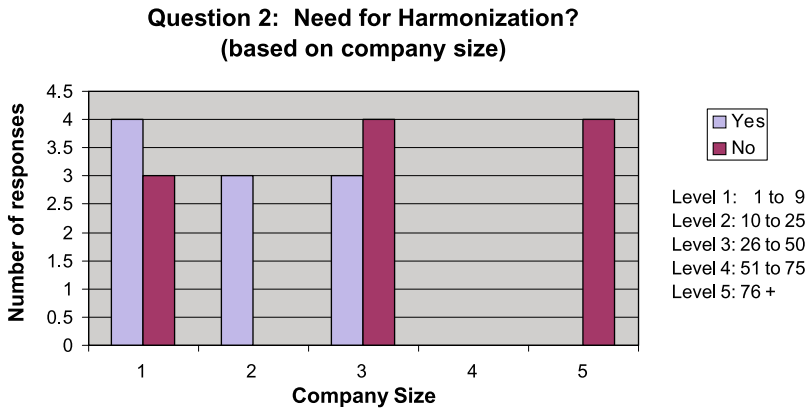

Fig. 3. Need for harmonization based on company size (level indicates products).

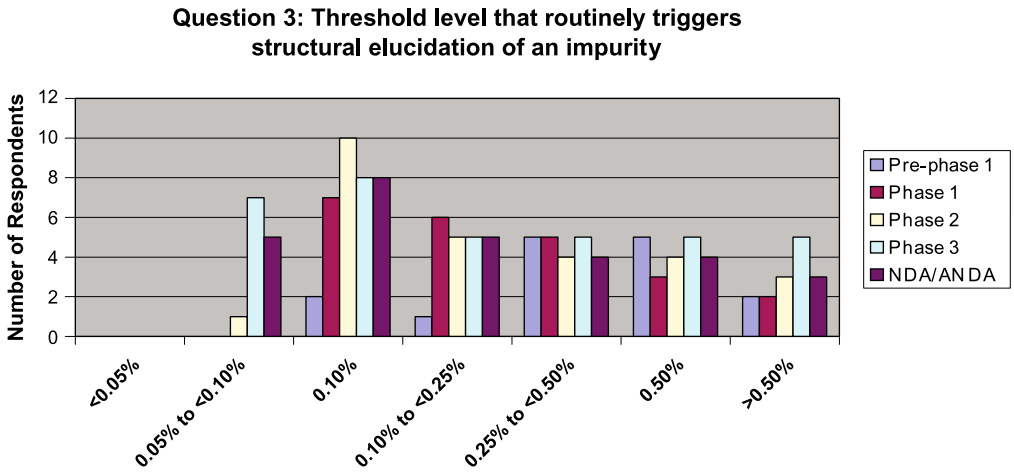

Fig. 4. Threshold level that routinely triggers structural elucidation of an impurity.

of the respondents felt a mass balance of 95% was sufficient, whereas 50% felt a mass balance of 90% was sufficient.

Question 8 asked what combinations of techniques are tried to achieve mass balance for samples subjected to ICH stability conditions. Forty-eight percent said they used HPLC, 20% used UV spectroscopy and MS, whereas 16% used LC–MS and gas chromatography (GC).

Quantification

The responses to question 9, "What typical method/s is/are used to quantify impurities?" are summarized in Fig. 6.

At prephase 1, 88% used LC–UV and 60% used GC–flame ionization detector (FID). For phase 1, 92% used LC–UV, 56% used GC–FID, and 40% used LC–PDA. For phase 2, 80% used LC–UV, 60% used GC–FID, and 36% used LC–PDA. At phase 3, 84% used LC–UV, 52% used GC–FID, and 40% used LC–MS (Fig. 7).

There is a 33% increase in methods used for impurity quantification from prephase 1 to phase 3.

Question 10 asked what calculation method is routinely used to quantify impurities at each of the phases (Fig. 8).

For prephase 1 and phase 1, most of the respondents used relative area percent for quantifying impurities. At phases 2 and 3, most used a response factor with a substantial number using a reference standard, although the majority used relative area percent throughout development. An internal standard was not a preferred method at any stage.

Question 11 asked what would cause the use of a reference standard earlier than reported in question 10. Sixty-four percent cited safety issues, 52% cited regulatory issues, and 32% cited different UV maxima and the level of impurities.

Table I gives the results of question 12 that asked about the appropriate level of validation at each stage of development. The number of respondents indicating a particular

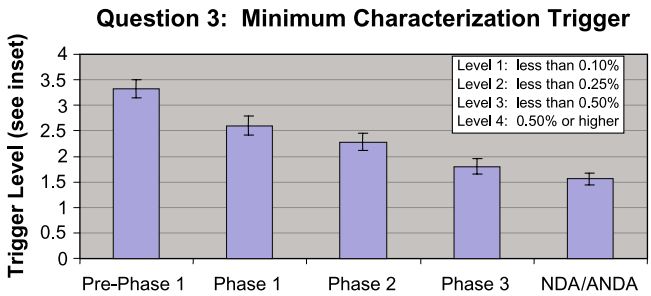

Fig. 5. Trigger level at each phase that initiates impurity characterization.

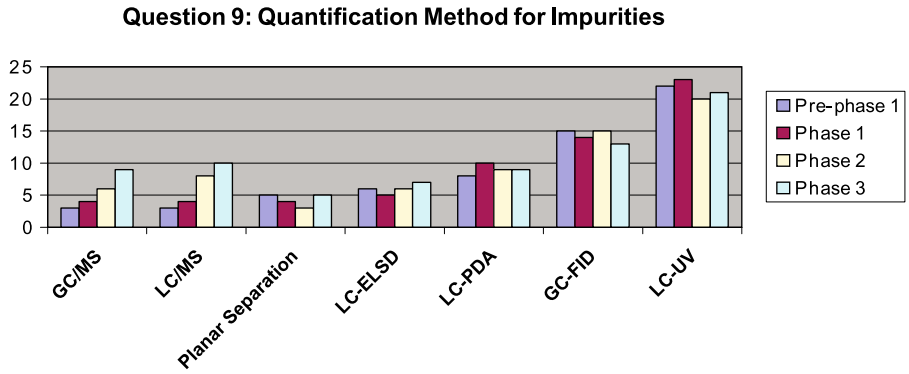

Fig. 6. Quantification methods routinely used to quantify impurities in each phase.

validation characteristic at each stage of development is reported as a percentage in the table. From Table I, it can be seen that "ruggedness/robustness" is not considered important until phase 2, whereas "specificity" is important at all stages. In general, more respondents increase the level of validation as drug development progresses from prephase 1 through phase 3.

Figure 9 illustrates the increase in level of validation or the number of validation characteristics addressed at each phase of development.

Question 13 asked if the respondents followed ICH guidelines for validation at early stages of development; 76% answered yes and 52% indicated they used internal guidelines. Shown in Fig. 10 is the breakdown of guideline use based on company size. There is a trend of utilizing internal guidelines as the size of the company increases.

Question 14 asked what robustness parameters are evaluated at each stage of development. The number of respondents indicating a particular criterion at each stage of development is reported as a percentage in Table II.

At prephase 1, 40% (highest percentage compared to other criteria) of the respondents used the stability of sample and standard for evaluation of robustness. At phase 1, in addition to stability, the mobile phase composition and mobile phase pH were also investigated. At phase 2, the impact of different analysts and instrumentation was added to what was done at phase 1. At phase 3, the evaluation of other columns was added to what was done at phase 2. Overall, significant increases in robustness testing occurred at phases 2 and 3.

Question 15 asked what additional techniques were used to assure that impurities with no chromophore were accounted for. Seventy-six percent responded they used LC–MS, 44% used thin-layer chromatography (TLC), and 36% used LC–refractive index (RI) method or LC–evaporative light scattering detector (ELSD). Additionally, 24% responded that they used conductivity, electrochemical detection, and derivatization techniques.

Question 16 asked how the respondent evaluates an impurity that has a different response factor from the parent. Sixty percent responded that they used UV–Vis spectroscopy.

Question 17 asked what additional techniques are used to assure no impurity is unretained, noneluted or coeluted. Eighty-four percent used an orthogonal method [e.g., normal phase chromatography, supercritical fluid chromatography (SFC), etc.]; 64% used LC–MS, LC–PDA, or mobile phase modification; and 48% used TLC.

Question 18 asked how the respondents cross-map (correlate) the impurities from various techniques. When using different methods, 40% used LC–MS to determine the identity of the impurities in each method, 28% isolated the impurities, and 28% used authentic materials or reference standards.

Question 19 asked how the respondents ensure that the methods are stability indicating for routine use. Sixty-four percent of the respondents challenged the method with known impurities and degradation products, 28% challenged the method with samples from stability studies, and 12% measured peak purity (PDA) to ensure that the methods were stability indicating.

Regulatory

Question 20 asked when complete structure elucidation is not possible, what data or rationale is provided at registration. Most respondents provided their best faith effort. They qual-

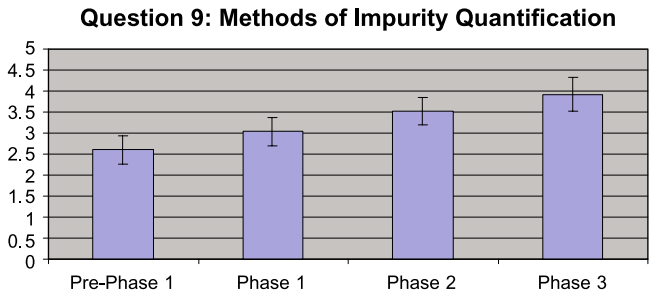

Fig. 7. The average number of methods used at each phase for impurity quantitation.

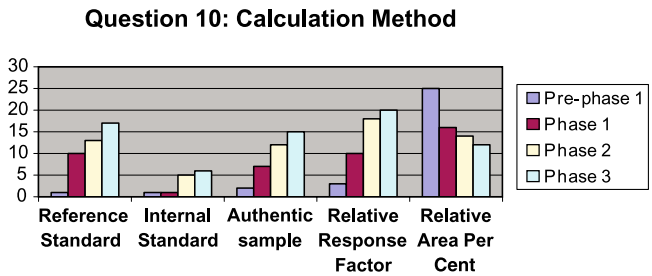

Fig. 8. Calculation method used to quantify impurities at each phase.

t1.1 **Table I.** Level of Validation at Each Phase

t1.2		Phase			
t1.3	Validation characteristic	Prephase 1	1	2	3
t1.4	Limit of detection (%)	40	56	64	92
t1.5	Limit of quantification (%)	40	76	72	84
t1.6	Linearity (%)	52	84	80	92
t1.7	Precision (%)				
t1.8	Intermediate (%)	8	48	60	92
t1.9	Repeatability (%)	24	60	68	92
t1.10	Accuracy (%)	28	32	64	92
t1.11	Ruggedness (%)	0	16	44	92
t1.12	Robustness (%)	0	16	44	100
t1.13	Specificity (%)	64	68	80	96

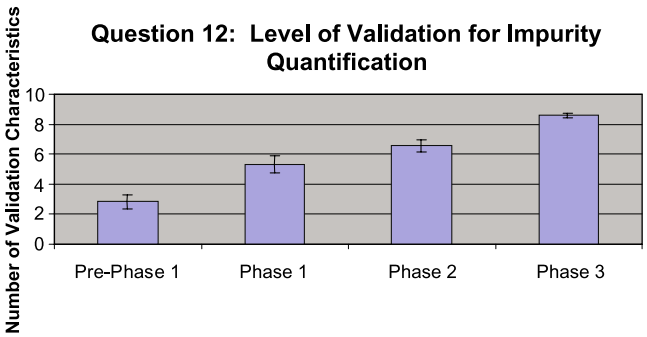

Fig. 9. The average number of validation characteristics addressed at each phase.

ified the impurity in safety/toxicology studies and/or they limited the amount of the impurity through synthesis/purification.

Question 21 asked the respondent to rank (on a scale of 1, regulatory, through 5, science) whether their answers to the survey were based on science or perceived regulatory requirements. The averages of the responses were 4.3 for phase 1, 3.4 for phase 2, and 2.2 for phase 3. This indicated that there is an appropriate trade-off between science and regulatory requirements depending on the phase of development.

Question 22 asked if the respondents believe that adequate, clear, and reliable guidance on impurities is available. Fifty-two percent of the respondents felt adequate, clear, and reliable guidance is available, 44% did not agree, 28% would like to see more information regarding specifications, 8% wanted more information on regulatory expectations, and 4% were interested in more information regarding chiral substances, leachables, and polymorphs (Figs. 11 and 12).

Demographics

Seven of the respondents worked in a company that had less than 10 products, three in a company that had between 10 and 25 products, seven in a company that had between 26 and 50 products, one in a company with 51 to 75 products, and four in a company that had greater than 75 products.

Twenty of the respondents worked in analytical R&D, three in pharmaceutical R&D, two in QA/QC, and one also worked in chemical R&D.

Five of the respondents worked in a department that had less than 25 people, eight in a department with 25 to 50 people, four in a department with 51 to 100 people, five in a department of 101 to 200 people, and two in a department with more than 200 people.

DISCUSSION

The low response to the survey should be kept in mind when evaluating the information provided in this report. However, it does seem clear that the respondents were generating data by taking into consideration good science and regulatory requirements. They increased the rigor of their approach as the drug passed through the stages of development and based these decisions more on science at the early stages of development and more on regulatory requirements at the later stages. It is the opinion of the Working Group that these decisions provided a good balance between science and regulatory requirements. Based on the survey results, the survey respondents do not recommend an additional guidance. The survey results and respondents suggest there may be a need for *further clarification* of

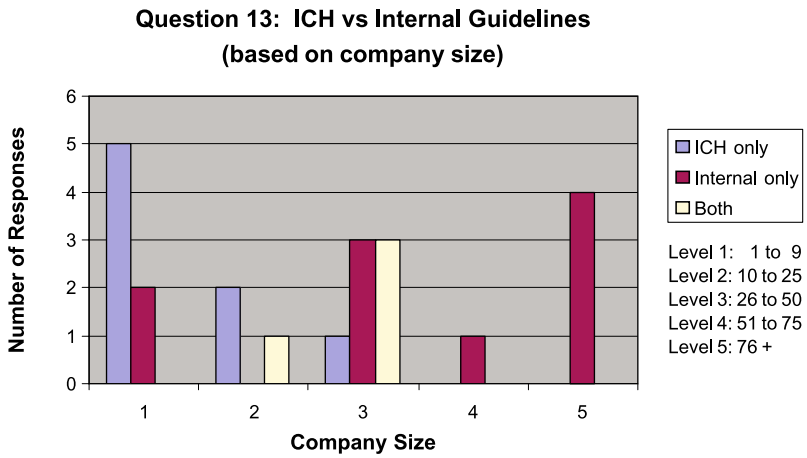

Fig. 10. ICH *vs.* internal guidelines based on company size (number of products).

t2.1 **Table II.** Robustness Parameters at Each Stage of Validation

		Phase			
t2.3		Prephase 1	1	2	3
t2.4	Mobile phase composition (%)	24	40	48	76
t2.5	Mobile phase pH (%)	20	44	48	80
t2.6	Alternate columns (%)	12	36	36	80
t2.7	Alternate instruments (%)	8	36	40	84
t2.8	Analysts (%)	8	24	44	84
t2.9	Stability of sample (%)	40	64	52	72
t2.10	Stability of standard (%)	40	60	52	68

requirements especially prior to the NDA for the identification of impurities, quantification, and validation of methodology and specifications. Readers of this report may provide further clarification to the PQRI. The results of the survey, although from a limited response, can be used by the reader as a basis for assisting with decisions at different stages of development.

The following conclusions can be drawn from the survey results with respect to the investigational new drug application (IND) stage of development.

1. Relative retention time is considered sufficient by respondents to characterize an impurity at the phase 1 IND.

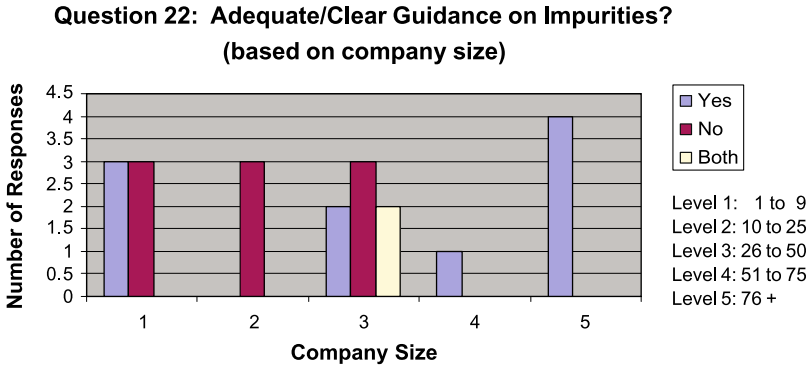

Fig. 11. Adequate and clear guidance on impurities.

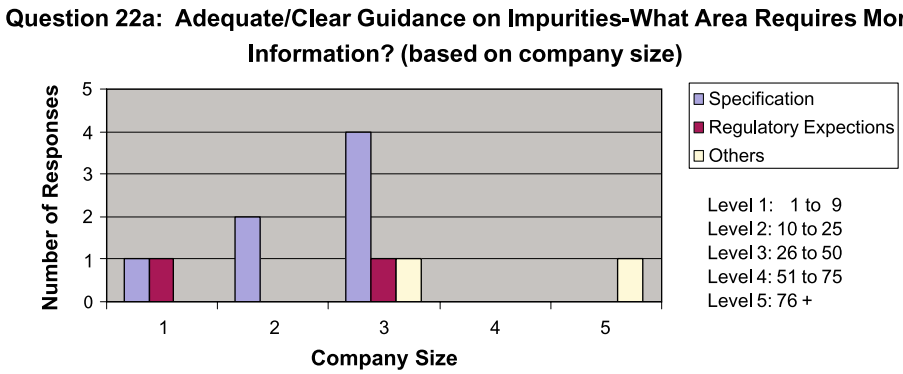

Fig. 12. Breakdown of additional information (specifications and regulatory expectations) *vs*. company size.

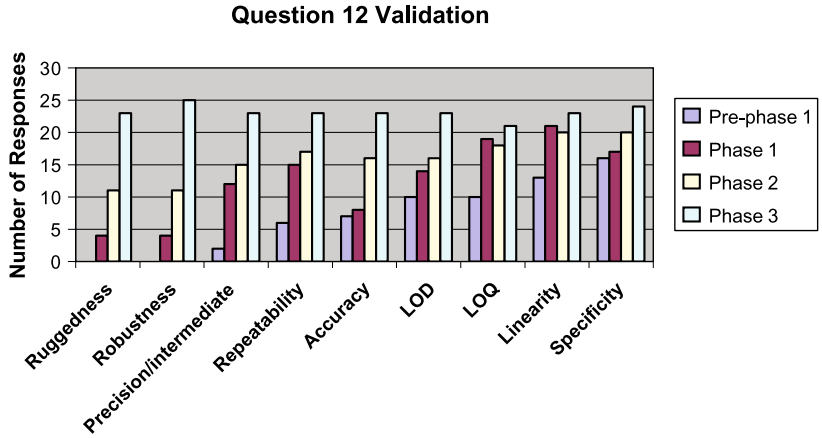

Fig. 13. Validation characteristics as a function of phase.

2. As the threshold for structure elucidation for IND, 0.5% is considered sufficient by respondents.

3. Purposeful degradation of API should be done for the IND.

4. LC and/or GC using area percent are considered sufficient by respondents to quantify impurities at IND (60% used area percent at phase 1).

5. Specificity, LOD, LOQ, linearity, repeatability, and stability of sample and standard were considered sufficient by respondents for validation for the IND (more than 50% used each of these criteria at phase 1).

6. There is a consistent, observed shift to increased rigor as development proceeds to Phase 3. This is evident in the answers to the questions for characterization methodologies (question 1), structural elucidation threshold (question 3), quantification methodologies (question 9), calculation (question 10), and validation requirements (questions 12 and 14) (Fig. 13).

One important issue that requires further clarification is related to the threshold for structure elucidation. There is an apparent disconnection between the current guidance for impurities and the answers given from what is required at NDA/ANDA. Several respondents indicated that a level of from 0.25 to greater than 0.5% was the threshold that *routinely* triggers structural elucidation.

CONCLUSIONS

Because there is a shift to increase in rigor during the development process and resources are allocated based on science at the early stages of development, we believe there is no need for a formal guidance regarding drug substance impurities at the early stages of development. There is an appropriate trade-off between science and regulatory requirements depending on the phase of development. In addition, the data presented in this publication may guide those groups who need direction on how to proceed.

The survey information was presented at the PQRI workshop, "Good Regulation Through Good Science" in August 2003 in Crystal City, VA. There was additional input from this workshop, including the hope for the Working Group to solicit more information from industry. Because the response to the survey was small, the Working Group would appreciate hearing from readers of this article regarding the need for additional guidance or any other topic that they feel is not consistent with their opinion or practice.