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Incentivizing Quality in the Manufacture of Pharmaceuticals: Industry Views on Quality Metrics and Ratings

Cesar Medina, MBA, MS, DRSc, RAC[1,2], and Frances J. Richmond, BNSc, MSc, PhD[1]

Abstract

Background: An increasing number of industry-wide quality breaches and consequential drug shortages have fueled interest in finding better ways to improve the manufacturing quality of pharmaceuticals. Quality metrics offer a way of focusing FDA inspectional resources by using risk-based paradigms and communicating the quality status of different companies to other stakeholders. This exploratory study investigated industry views related to the use of quality metrics and ratings to help advance these discussions. *Methods*: A 23-question survey engaged 2 separate populations of industry professionals: a panel of identified US industry experts (n = 110) and a broader population (n = 328) of professionals working primarily in southern California. *Results*: FDA metrics most valued by industry were warning letters and other observations, often characterized as "lagging" metrics. Respondents were generally hesitant to share information that would establish "leading" metrics, such as process performance measures that may warn of problems earlier. Ratings were recognized to incentivize higher quality by broadening stakeholder influence. However, concerns were identified related to the equity, misuse, or misunderstanding of the rating schemes and underlying metrics. *Conclusions*: Industry is an important stakeholder in the development of metrics. The concerns of industry must be recognized and addressed if policies related to metrics and ratings are to be effective in building an industry-wide quality culture.

Keywords

GMP, metrics, scorecards, incentives, drug shortages

Introduction

Quality problems in the manufacture of pharmaceuticals are troublesome for many reasons. They not only risk harm to patients but also require manufacturers to expend valuable resources on investigating and correcting the problems. Problems that must be corrected by halting production result in unfilled purchase orders and loss of potential sales revenue. These interruptions can also lead to drug shortages, putting patients in harm's way if their treatments must be delayed or if their medications are replaced with suboptimum substitutions. Thus, much can be gained when companies have strong quality systems. However, industry-wide quality problems and drug shortages remain stubbornly high, and quality breaches are often not detected until the defective products are released into the marketplace.[1-3] Regulators and industry have recently tried to find better ways not only to improve compliance with current regulatory quality standards but to go beyond those minimum standards by building an industry-wide quality culture.

US Regulatory Oversight and Enforcement (GMP)

In 1962, the Kefauver-Harris Amendments strengthened the drug adulteration elements of the US Federal Food, Drug and Cosmetic Act of 1938 (FDCA) by requiring manufacturers to comply with good manufacturing practices (GMPs). Compliance with these regulations is typically judged by manufacturing site inspections. Until recently, the FDCA mandated that FDA conduct GMP inspections biannually for domestic

[1] International Center for Regulatory Science, School of Pharmacy, University of Southern California, Los Angeles, CA, USA
[2] Global Regulatory Affairs CMC, Amgen Inc, Thousand Oaks, CA, USA

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Corresponding Author:
Cesar Medina, International Center for Regulatory Science, School of Pharmacy, University of California, 1540 Alcazar Street, CHP 140, Los Angeles, CA 90089-9014, USA.
Email: cesarmed@usc.edu

manufacturers with no such stipulation for foreign manufacturers.[4] However, the US FDA's inspection system has become strained as the number of new drugs continue to increase and manufacturers expand their operations abroad. Thus, many manufacturing sites, particularly foreign sites, are inspected infrequently and some are not inspected at all.[5] To alleviate FDA's inspection burden and help place inspectional resources where they are needed most, regulators and industry have turned to a risk-based inspectional approach so that sites with a history of noncompliance will have more frequent comprehensive inspections than those with a proven record of quality compliance.[6] In 2012, the passage of the Food and Drug Administration Safety and Innovation Act (FDASIA) included the mandate and resources for FDA to formalize and implement a risk-based inspection program.[4] To carry out such an approach, however, regulators need a system for rating and comparing manufacturers based on an equitable set of metrics. The FDA has previously attempted to develop a risk-ranking model by using its repository of inspection outcomes,[7] but a transparent, equitable, and consensual quality evaluation framework that determines the frequency of site inspections using a risk-based approach has not yet been developed.

Discussions of quality risk-rankings have also raised questions about the effectiveness of GMP inspections as a means to encourage high quality in manufacturing. The GMP regulations for pharmaceuticals establish minimum requirements to ensure that products are safe and effective but do not provide an incentive for manufacturers to go beyond that minimum benchmark and strive for excellence in quality. In economic terms, enforcement of GMPs works as a one-sided *incentive-based regulation* whereby the manufacturer must comply with the standards in order to sell its products but is offered no reward for exceeding them. Some companies may elect to exceed GMP standards because they recognize, as do companies in other industries, that there is a "cost to poor quality" that can be minimized through a solid quality system. Nevertheless, when business decisions are tied to the current manufacturing and market dynamics that focus on reducing overhead costs and drug prices, a "race to the bottom" can ensue where GMP compliance becomes the only target.[8-12] These forces are most prevalent in the generic sector, where manufacturers sell their products in a marketplace that is often crowded with competitors and is driven by low pricing, low profit margins, and unpredictable consumption, and where manufacturers have few options to differentiate product quality.[8,10-14] In this environment, manufacturers have little incentive to invest in quality through such actions as upgrading facilities or training additional staff. Some industry analysts have concluded that this poor incentive structure has been responsible, at least in part, for the persistent quality problems and the recent rise in drug shortages.[8-12]

Views on Improving Quality Incentives

Several options have been suggested to provide incentives that would improve manufacturing quality. For example, Villax recently[15] suggested that FDA establish a "FDA Dean's List" of companies that go beyond the minimum standards and that FDA share this information publicly in order to recognize high quality. Others have suggested mechanisms such as rating scales to make quality more visible to buyers, who then could decide whether the higher quality would be worth a commensurately higher price.[8,10,16] Still others have suggested that companies with a strong record of quality be given shorter regulatory review periods or other preferential regulatory treatments.[17-19] All of these alternatives share a perceived need for a pharmaceutical quality rating system and acknowledge the motivational value of publicly sharing more information on quality.

Pharmaceutical Quality Rating Systems

Regulators and industry have suggested that the differences in the manufacturing quality of products and companies be made more visible to motivate investments in superior quality systems,[8,12,16,18] as has been done in other industries. For example, restaurants and hospitals use scorecards that allow customers to make informed buying decisions.[20,21] A few organizations, including the FDA, have discussed the metrics that could potentially be measured for the limited purpose of assisting FDA in developing a risk-based inspection framework.[6,22] A broader engagement of industry is important, however, if such measures are to be accepted as credible by the many types of manufacturers that will be affected by risk-based inspections and quality ratings.

The primary purpose of this exploratory study was to better understand industry's views on the use of quality metrics and ratings. We further explored the potential impact that quality ratings may have on company quality practices and whether such measures would incentivize manufacturers to increase their investments in quality. An initial driving force for the research was the work of the Quality Leadership Network (QLN), a public-private workgroup organized through the US FDA Los Angeles District Office (Irvine, California, USA). The QLN's efforts to explore the extent of use of quality information stimulated the codevelopment of a web-based survey open to a range of professionals from different backgrounds and job levels within the local area. The QLN survey was supplemented further by conducting a parallel targeted survey of industry experts across the United States whose inclusion in the survey was based on specific criteria.

Materials and Methods

A survey instrument with 23 questions engaged two populations of US medical product manufacturers in separate panels.

The first was the expert panel of professionals working at middle to senior management levels with substantial expertise in the subject matter, who were identified through professional networks, conferences, professional associations (eg, American Society of Quality (ASQ), International Society for Pharmaceutical Engineering (ISPE), Parenteral Drug Association (PDA), IQ Consortium), and reliable referrals. The links given to this panel were unique to the chosen participants, so that the links could not be shared beyond the identified individual. The second panel was derived from associates and contacts of the QLN, which represents a broader population of FDA-regulated industry professionals working at different job levels and in different sectors of the pharmaceutical, device, food, and raw materials supply industries. An anonymous open-access link to the survey was sent to this target population. No remuneration was paid to the respondents, but they were ensured anonymity and offered a summary of the results to encourage their participation.

The survey instrument was developed in consultation with members of the University of Southern California (USC) International Center for Regulatory Science and the QLN, who provided feedback on the content, flow, and clarity of the questions. The survey was distributed using Qualtrics online survey software. A near-final survey was piloted by a subset of the QLN to evaluate the functionality of the software, the content validity of the questions, and the response rates for its various questions. The survey was finalized (see the supplementary online material for this article) and deployed to the expert and open-access panels and remained open from June 2 to July 20, 2014. The expert panel survey collected 110 responses with a completion rate of 85%. The open-access survey collected 328 responses; 246 individuals completed at least the first two-thirds of the survey, and 178 completed the entire survey. All answers to questions were accepted for analysis regardless of whether all questions in the survey were answered. However, 4 individuals in the expert panel communicated that they were not well suited to participate, and their responses were removed at their request. Responses to scaled questions within each survey were described by the number of responses, percentages, means, and standard deviations. Comparisons from one survey to the other were carried out using chi-square methods for discrete data and *t* tests or Wilcoxon tests for continuous data, but the relatively small numbers in this exploratory study precluded the demonstration of all but strong differences between the 2 surveys.

Results

Demographics

Both the expert panel (EP) and open-access (OA) surveys drew respondents from companies with different product mixes and different geographical areas. Most respondents from the expert panel worked at companies manufacturing pharmaceutical drugs and biologics (72%), whereas half of the respondents from the open-access survey worked at medical device companies (51%) (Table 1). Over half (62/108) of the EP respondents worked for large companies (>5000 employees) distributed widely throughout the United States (70/107) or Europe (20/107). The OA respondents represented companies with a more even distribution of sizes (1-250 employees: 128/293; >1000 employees:113/293), mostly (213/292) located in "West Coast, USA." Respondents in both groups mostly held positions in quality management and regulatory affairs and a modest number of research and development scientists and manufacturing operations managers (Table 2).

Table 1. Most recent employer of respondents.

	Expert Panel		Open-Access Survey	
Description	No.	%	No.	%
Manufacturer of pharmaceutical drugs/biologics (innovator/branded)	78	72	61	21
Manufacturer of pharmaceutical drugs/biologics (generic)	13	12	13	4
Manufacturer of pharmaceutical raw materials (API, excipients, reagents, containers)	12	11	4	1
Manufacturer of cosmetic products	1	1	5	2
Manufacturer of dietary supplements	1	1	6	2
Manufacturer of food/nutritional products	1	1	6	2
Manufacturer of medical devices (including IVDs)	7	6	150	51
Contract manufacturer/services	13	12	26	9
Regulatory agency/government body	0	0	6	2
Analytical laboratory or other testing services	1	2	4	1
Distributor or wholesaler of medical products	2	2	11	4
Other	9	8	54	18
Total responses	108	100	296	100

Respondents were allowed to select up to 2 choices. API, Active pharmaceutical ingredient; IVD, In vitro diagnostic.

Manufacturing Quality Metrics

Respondents reported the use of several types of metrics. The FDA website was typically consulted on a weekly or monthly basis, particularly for warning letters and FDA Form 483s, which were considered by both the EP and OA groups as "very important," whereas the drug shortage index was rated as being "least important" (Figure 1) of the provided options. Use of FDA field corrective actions was significantly higher ($P < .001$) for the OA than EP respondents. Most of the non-FDA sources of information offered as options in the survey were typically consulted more commonly by respondents of the EP than the OA panel but tended to have similar distributions of preference. However, OA respondents more commonly

Table 2. Primary occupation of respondents.

	Expert Panel		Open-Access Survey	
Description of Primary Occupation	No.	%	No.	%
Manufacturing engineer or scientist	3	3	3	1
Research and development scientist	13	12	11	4
Manufacturing operations management	6	6	17	6
Quality management	41	39	113	39
Supply chain management	0	0	4	1
Regulatory or legal affairs	30	28	99	34
Business consultant	3	3	9	3
Other	10	9	33	11
Total responses	106	100	289	100

inspected company websites (61%) than did EP respondents (46%) (Table 3).

When asked about public or proprietary information and given a selection of metrics that might be used to assess quality, the EP respondents most commonly selected information about noncompliance trends (75%), whereas OA respondents placed more emphasis on customer complaint rates (80%) and the number of corrective actions taken (70%) (Figure 2). Product defect rates had similarly high selection rates (EP 64%, OA 65%). Identified as "other" commonly used metrics were process performance measures (eg, lot rejection and acceptance rates), internal quality audits, product risk assessments, and health agency outcomes (eg, first cycle approvals and inspection observations).

When questioned about the metrics that their company might hypothetically be willing to share to help improve industry-wide quality under conditions of anonymity, the top metrics selected by the expert panel were raw material supplier metrics (38%), complaint rates (37%), and process performance indicators (32%). The open-access group expressed more willingness to share metrics associated with the number of corrective actions taken (43%), complaint rates (39%), and raw material supplier metrics (38%). The metrics that companies would be least willing to share publicly were product rejection (26%) and return (18%) rates by the expert panel, and product rejection (20%) and manufacturing error (17%) rates by the open-access group (Figure 3). The most common answers entered as "other" in an open-text field were either that they were not in a position to answer this question or that no information could be currently shared (number of comments: EP 13, OP 12).

Impact of Ratings on Quality Improvements

The personal views of the respondents were probed with regard to the ways in which quality ratings might affect company and consumer decision making. The expert panel and open-access groups indicated a high level of agreement and a high level of congruence on the effect that quality scorecards might have and suggested that the quality ratings might be particularly influential on manufacturers (Figure 4). Both the EP and OA respondents predicted that the strongest effects would be seen on internal and supplier quality audits, employee training, and the emphasis on quality as a more company strategic goal but typically would have "little impact" on company decisions to open additional manufacturing sites (Figure 5).

Policy Views on Quality Ratings

A series of questions were posed to gauge the respondents' personal views on policy initiatives that relate to quality rating systems. When asked to identify what they "perceived to pose the most challenges in interpretation of a manufacturing quality grade" from a selection of options, many respondents felt that consumers may misinterpret a grade as an assessment of overall product safety (EP 71/93, OA 116/170) or mistake it as a measure of clinical benefit (EP 50/93, OA 93/170). Relatively fewer expressed the concern that an otherwise safe product would not be used because it had been assigned a lower grade (EP 29/93, OA 70/170) or that consumers would choose to ignore the grade altogether (EP 25/93, OA 33/170). When asked about the amount of information that consumers would need to interpret a quality grade from a selection of options, most respondents believed that the quality grade alone (EP 71/92, OA 122/175) and a description of the key metrics associated with the grade (EP 50/92, OA 126/175) would be most informative. The majority of respondents (EP 61/92, OA 121/177) also indicated that if grades were issued, public disclosure should be mandatory, and they ranked FDA as their first choice to be the organization best-suited to issue the grade from a selection of options (EP 46/84, OA 62/156).

Open-text questions were placed throughout the survey to capture additional thoughts that respondents might have had. Many respondents voiced disagreement with any policy to make quality ratings public. The reasons given for these views included concerns that quality metrics would not be equitable, fair, or representative of quality across product and company types; concerns that public grades may incorrectly and irreversibly tarnish the reputations of smaller companies over larger ones; views that quality ratings would not improve quality but only increase costs or result in undesired behaviors (eg, "gaming the system"); views that the need for quality improvement or metrics is not required or justified; concerns about associated legal liabilities; and opinions that consumers are not in a position to make decisions regarding pharmaceutical quality.

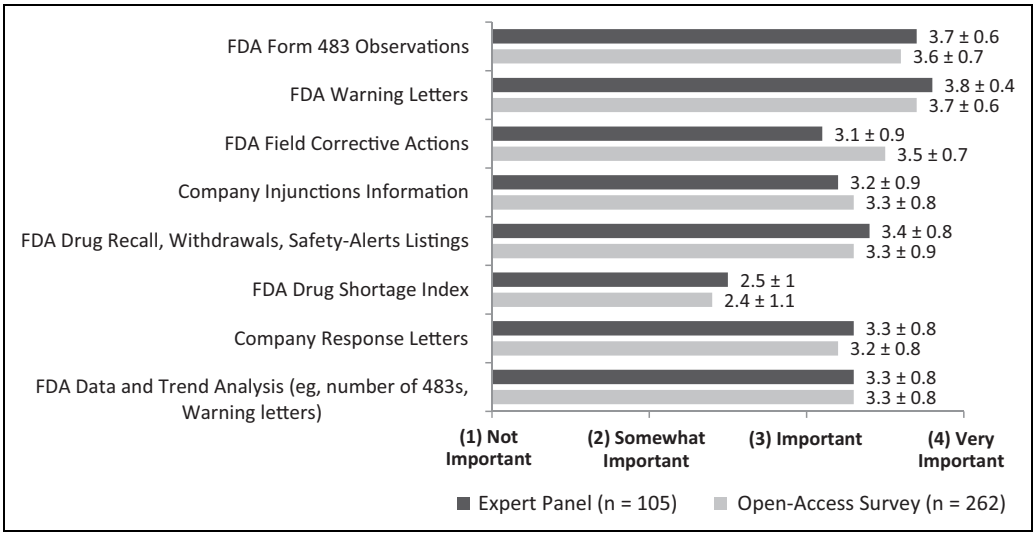

Figure 1. Level of importance placed on FDA available information (mean ± standard deviation). Respondents were asked to rate the importance of listed information in making quality evaluations of their company, partners, competitors, or suppliers.

Table 3. Public sources other than FDA used to obtain information on product and company quality.

	Expert Panel		Open-Access Survey	
Description of Source	No.	%	No.	%
Trade or industry group (eg, PhRMA, BIO, EFPIA, AdvaMed)	84	79	174	71
Pharmaceutical professional organizations (eg, ASQ, ISPE, PDA, MDDI)	89	84	127	52
Educational resources (eg, journals, white papers, universities)	73	69	148	60
Other governmental websites (eg, WHO, EMA)	72	68	105	43
Drug index, formulary, supplier listings (eg, orange book, drugs.com, qmed.com)	30	28	44	18
Company websites	49	46	150	61
Public reputation (ie, word of mouth)	38	36	108	44
Other	22	21	31	13
Total responses	106	100	246	100

Respondents were allowed to select all that applied. EMA, European Medicines Agency; WHO, World Health Organization; PhRMA, Pharmaceutical Research and Manufacturers of America; BIO, Biotechnology Industry Organization; EFPIA, European Federation of Pharmaceutical Industries and Associations; AdvaMed, Advanced Medical Technology Association; ASQ, American Society for Quality; ISPE, International Society for Pharmaceutical Engineering; PDA, Parenteral Drug Association; MDDI, Medical Device and Diagnostic Industry.

Discussion

This study explored how manufacturers currently use quality metrics to benchmark their activities and their views on the use of visible quality ratings to announce their quality status. We focused on manufacturers as a critical stakeholder because they are active participants in the development and collection of manufacturing metrics, they hold expertise in manufacturing operations and quality management, and ultimately they make decisions regarding their firm's quality direction. The 110 respondents in the expert panel represented a small, but nonetheless highly qualified, population of professionals working predominately for large pharmaceutical manufacturers (72%) located throughout the United States and Europe. The respondents of the less restrictive open-access survey worked primarily for medical device (51%) manufacturers rather than pharmaceutical (21%) manufacturers and were primarily in California. Perhaps surprising was the high degree of congruence between most responses provided by these two rather different groups. Where differences seemed apparent, for example, the preference of OA respondents for FDA field corrective actions or the number of corrective actions taken as a metric of quality, these differences might be related to the nature of manufacturing and support practices associated with device rather than pharmaceutical operations. The OA group was largely drawn from California, an area of enriched device company presence, but it is not clear whether the practices in California differ from those elsewhere in the United States. An exploratory tool of this type is only able to point to areas in which further exploration might be warranted. However, the relatively similar overall response patterns from one survey to the other suggest that views among subpopulations are not greatly different and further suggest a certain amount of external validity at least across US industries.

A clear message from this study was the value that industry places on FDA quality measures and information, particularly on records associated with FDA's inspectional actions such as warning letters and inspectional observations documented

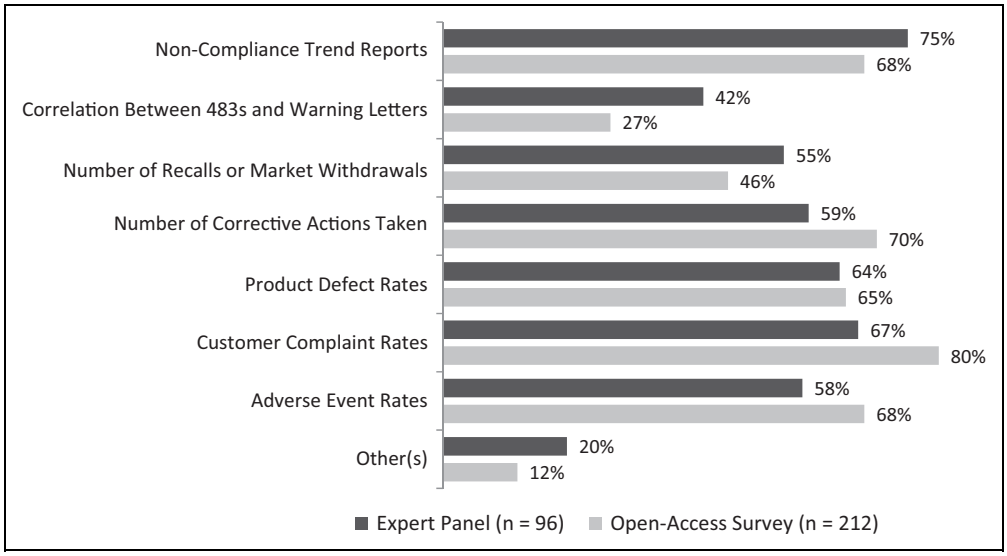

Figure 2. Metrics commonly used to assess company and product quality.

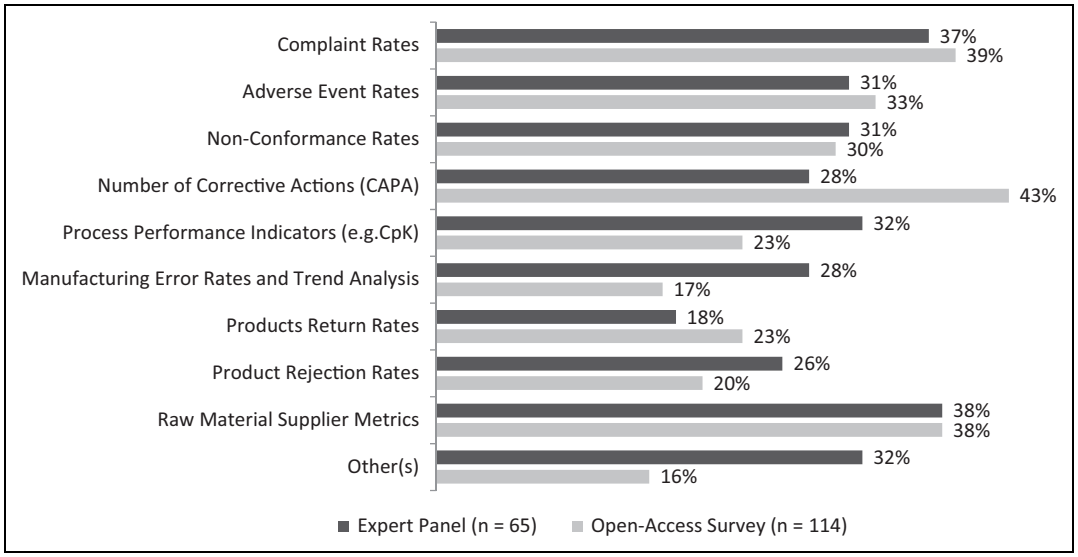

Figure 3. Metrics that companies might be willing to share anonymously for industry quality improvement efforts.

in "FDA 483s." Interestingly, the metric designated to be the least important was related to drug shortages. It would be valuable to understand how those who are affected more directly by drug shortages, such as pharmacies and patients, would view drug shortages as an informative metric, and whether considerations of drug shortages might be a more important policy driver for FDA than industry as ranking systems are developed. Industry also seems to place a strong value on its reputation with customers, as reflected by the commonly selected metric of customer complaint rates in this study. Perhaps not surprisingly, customer complaints have been high on the list of quality metrics that FDA is considering for risk-based inspections.[6]

Customer complaint rates, like warning letters or product recalls, are lagging indicators of quality. Some analysts have suggested that greater value might be gained through the collection of leading metrics such as process performance measures that provide an early warning of quality problems.[6,22] However, this study suggests that manufacturers may not be enthusiastic about sharing leading metrics such as manufacturing error rates and product rejection/return rates. A reluctance to share quality information more generally appeared to be reflected by the fact that of all questions asked in the survey, the question probing what quality metrics might be shared was the least commonly answered and text responses often identified that the company was not prepared to share any

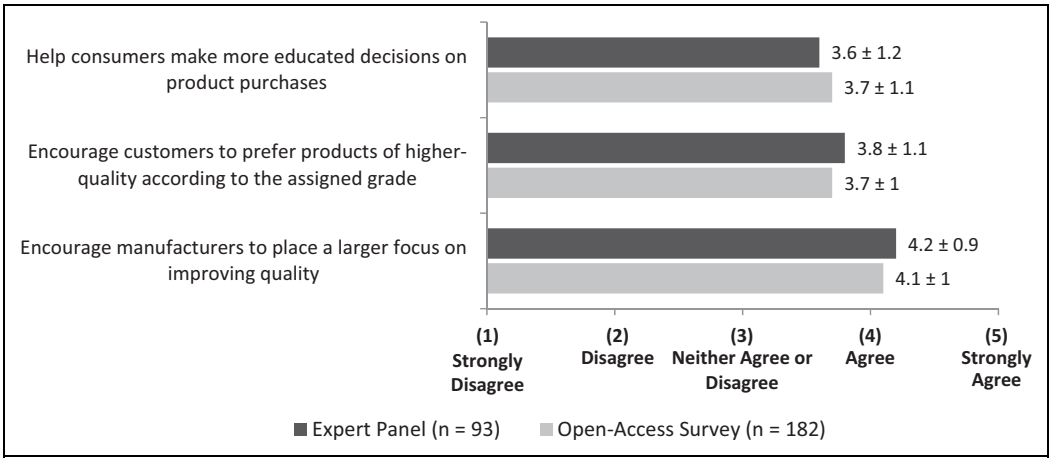

Figure 4. Level of agreement on how quality valuations might be influenced by quality ratings (mean ± standard deviation).

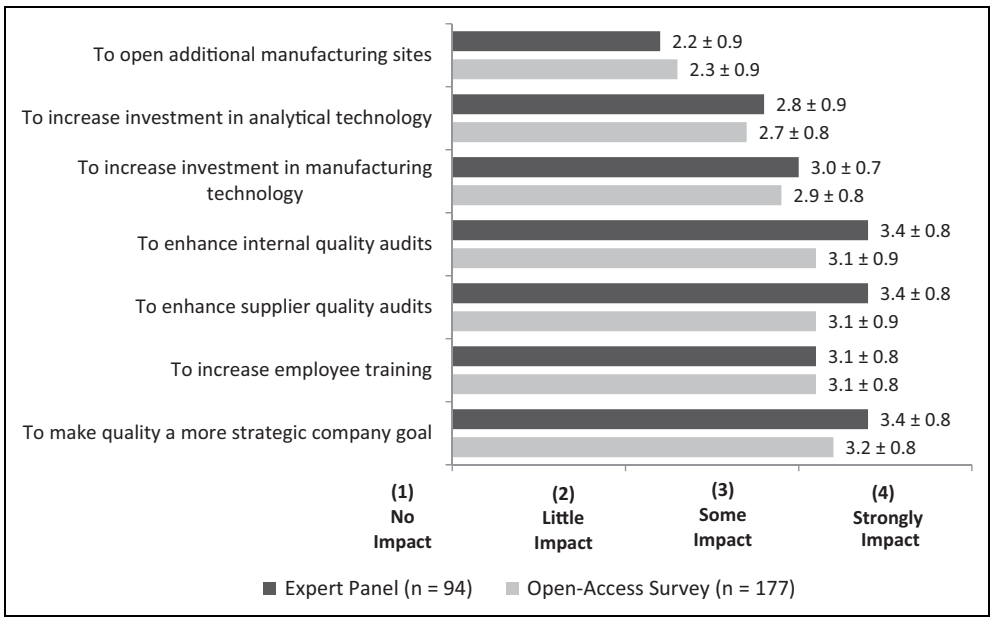

Figure 5. Impact that quality ratings may have on company decisions (mean ± standard deviation).

information. This study also suggests that device manufacturers may use metrics differently than pharmaceutical manufacturers, and this difference should be explored in more detail before quality metrics used by the pharmaceutical industry are considered appropriate to measure quality in other subsectors governed by FDA. Industry is a critical stakeholder whose positions on the use and sharing of certain kinds of information will need to be explored and taken into account as FDA attempts to develop new metrics derived from company supplied data.

This study also sought to understand industry views on the impact that visible quality ratings may have if such a policy was enacted. In a highly competitive industry where company reputation matters, it was not surprising that visible quality ratings were predicted to encourage "a larger focus on improving quality." However, it seems likely from the survey feedback that these investments would be targeted to specific aspects of quality improvement; most respondents predicted higher investments in their quality audit programs and employee training than in capital expenditures such as buying new equipment or opening new manufacturing sites. Responses suggest that a visible scorecard reflecting quality may incentivize investment in quality, as has been experienced in other sectors,[20,21,23,24] but additional inquiry within industry as well other stakeholders such as buyers and group purchasing organizations is needed to affirm whether these investments will achieve the

objective of attaining a quality culture rather than simply gaming the system.

As with any evaluative framework (eg, educational assessments and business improvements), early engagement and attaining buy-in from critical stakeholders are recognized to be prerequisites for success.[25] In this study we find some doubt in the minds of the respondents that quality metrics and quality ratings would result in quality improvements. Although the majority of respondents agreed that if grades were issued firms should be mandated to disclose those grades, respondents also expressed concerns that consumers may not comprehend the grade or may mistake it as a sign of overall product safety or clinical benefit. These observations are not dissimilar to those identified a decade ago by the Institute of Medicine, which found that almost half of US adults have difficulty understanding health information.[26] These observations may temper the predominant view that ratings would help consumers to make more educated decisions and to choose products from companies rated as higher in quality. Perhaps focus group sessions with manufacturers and consumer representatives would help provide a deeper understanding of what might be a serious limitation of a visible rating system. Another industry concern found in this study is that the selection of metrics that will be purported to reflect quality may be misleading or inequitable across the many types and sizes of companies that comprise the medical product industry; this sentiment is echoed in other evaluations of quality metrics and has yet to be resolved.[6]

Conclusions

Inarguably, GMP regulations have greatly improved the quality of drugs since their inception, but currently there is no compelling regulatory or market incentive for going beyond GMP compliance. In an industry with little tolerance for product defects or shortages, efforts on part of regulators and industry to "move the needle" when it comes to quality are imperative. However, any approach to make quality information more visible to the public or within industry would be a major departure from current regulatory policy. FDA's legal obligations to avoid the disclosure of proprietary company information limit the extent to which quality metrics can be shared with the public.[6] Thus, voluntary disclosure would be much simpler to achieve because mandated disclosure would require broader policy reform. Early engagement of pharmaceutical manufacturers, as was the focus of this study, is thereby critical for adding a greater level of credibility to any such policy decisions.[27,28]

The findings in this study support the premise that visible quality ratings may be one way to encourage and incentivize quality in the manufacture of pharmaceuticals. However, the first likely step is for the use of rankings by FDA to sort companies for risk-based inspections. In such a system, manufacturers might be incentivized both by a reduction of inspections and potentially by the ability to communicate their quality status to others. Additional regulatory incentives such as reduced review periods are also foreseeable. Although one of the main challenges seen with making ratings public is that consumers would not understand the rating, communicating this information in an understandable manner may help broaden consumers' influence in the marketplace by allowing them to choose higher-quality products. Additional research is needed to understand how patients may use quality information to decide what medical products are best for them. Gaining an understanding of how wholesalers and group purchasing organizations can use quality information is also recommended since they are largely responsible for supplier selection and price negotiation in the pharmaceutical supply chain. If market incentives are sought as a means to increase investment in quality, empowering more stakeholders with quality information is needed to shift from a limited one-sided regulatory-compliance incentive structure to one that is more closely aligned to the market-driven incentives found in other industries.

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Supplementary Material

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