

## Results of a Survey of Biological Drug and Device Industries Inspected by FDA under the Team Biologics Program

STEVE BUCHHOLZ, PH.D.,<sup>1</sup> VICTOR J. GANGI,<sup>2\*</sup> ANNE JOHNSON,<sup>3</sup> JACQUELINE LITTLE, PH.D.,<sup>3</sup> STEVEN MENDIVIL,<sup>4</sup> CAROLYN TROTT,<sup>5</sup> KEITH WEBBER, PH.D.,<sup>3</sup> MARK WEINSTEIN, PH.D.<sup>3</sup>

<sup>1</sup>Pfizer, Inc., <sup>2</sup>Wyeth Biopharma, <sup>3</sup>US FDA, <sup>4</sup>Amgen Inc., <sup>5</sup>Genzyme Corp.,  
Product Quality Research Institute Work Group

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**ABSTRACT:** The Product Quality Research Institute, in conjunction with the Food and Drug Administration, conducted an anonymous, electronic survey of the biological products manufacturing industry inspected by Team Biologics, with emphasis in obtaining industry input on inspection and compliance aspects of program operations. Representatives from all of the product-specific manufacturing industries inspected under the Team Biologics Program responded to this survey (vaccines; fractionated plasma proteins and recombinant analogs; allergenics; therapeutics and in-vivo diagnostics; and in-vitro diagnostics, including blood grouping reagents).

Data and written feedback was obtained regarding each firm's interactions and experiences of Team Biologics inspections at its facilities over the past three years. The three areas most impacted by Team Biologic inspections were "Production and Process Controls", "Failure Investigations" and "Facility / Equipment Controls". Overall assessment of the program was generally positive with 68% identifying a positive impact on the sites operations and 88% assessed the inspections as being conducted fairly. The findings and conclusions of this report will be utilized by the FDA to evaluate and further assess the impact of the Team Biologics Program and to implement any necessary changes. This report provides useful information to companies currently manufacturing licensed biologic products subject to Team Biologics inspections and also to those companies anticipating these inspections for future product manufacturing.

**KEYWORDS:** FDA, GMP inspections, Survey, Team Biologics

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### Background

In 1997, a partnership between the Office of Regulatory Affairs and the Center for Biologics Evaluation

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\*Corresponding Author: Victor J. Gangi, Director CMC, Regulatory Affairs, Wyeth Biopharma, 1 Burt Road, Andover, MA 01810. Phone 978-247-4756, Fax: 978-684-4856, E-mail: gangiv@wyeth.com  
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and Research (CBER) was formed to bring the Food and Drug Administration (FDA) regulatory approach for the biologics industry in line with other FDA centers. The goal of this partnership, called Team Biologics, was to ensure the quality and safety of biologic products, resolve inconsistencies, and bring manufacturers into compliance. One aspect of the Team Biologics Program focuses specifically on inspection and compliance for CBER-regulated devices and biological drugs (vaccines, allergenic extracts, fractionated plasma, and therapeutic products).[1] In July 2003, the regulatory authority for biological therapeutic products was transferred to the Center for Drug Evaluation and Research; however, these products continue to be inspected by Team Biologics.[2]

In 2002, the FDA conducted an in-depth internal evaluation of the Team Biologics Program. This evaluation, designed to review, assess, and improve program

operations, resulted in the formation of several initiatives, some of which have been implemented or are currently underway. These plans, which align with the agency's *Pharmaceutical CGMPs for the 21<sup>st</sup> Century* initiative, include developing and adopting a quality policy; conducting standardized training for investigators and center scientific experts; and implementing enhanced risk-based work planning principles.[3]

The FDA decided that industry input was essential for implementation of an additional initiative that focused on developing metrics to further evaluate Team Biologics' effect on industry and to measure its impact. To reach industry, the FDA partnered with the Product Quality Research Institute (PQRI) to develop a survey that allowed for feedback from the biologics industry on inspection and compliance aspects of the Team Biologics Program. An analysis was performed by the PQRI Work Group and the results are discussed in this report, with individual company responses remaining anonymous.

### Description of Methods

The survey was developed by a PQRI work group comprised of both industry and FDA representatives and was designed to assess the impact of Team Biologics inspections conducted over the past 36 months. The Biologics Inspection Survey consisted of 29 questions to gain industry feedback on general inspection practices, inspection focus, actions taken by the firm as a result of Team Biologics inspections, compliance follow-up, and overall interactions of Team Biologics with the industry. The use of complex statistical methodology was not appropriate due to the number of responses obtained for individual industry product type. Trends were assessed and analyzed by numerical percentage calculations. The types of questions included open-ended response and close-ended or fixed response (multiple choice or numerical, for example).

The on-line survey was announced in a letter mailed to FDA registered domestic and foreign locations of firms that manufacture biological drug and device products and routinely receive current good manufacturing practice (CGMP) inspections by Team Biologics (a single firm may have multiple sites). The announcement letter was addressed to the head of quality and mailed to 163 registered manufacturing sites on January 23, 2006. The letter contained a website address and a numeric password required to access the survey. The availability of the survey was also widely

announced through several methods including industry and public meetings, broadcast e-mails to trade organizations, and in articles posted on both the PQRI website and in the *Parenteral Drug Association Newsletter*. The survey was accessible 24 h a day for over a 4-month period, from January 23 to May 31, 2006. To assure complete confidentiality of the respondents, an independent contractor (Valtera Corporation, Rolling Meadows, IL) managed the internet survey and data collection. This report is based on data from 42 surveys; 37 surveys were fully to mostly complete and five contained minimal but sufficient information to be included in the final analysis. The minimum inclusion criteria were a valid firm/site from the original list of 163 sites and at least four questions answered. The response rate represented 26% (42/163) of the targeted audience. Because not all respondents answered all questions, there are differences in the total number of responses for each question. Also, because as the survey was addressed to the attention of the head of quality at the registered site, the responses and comments likely reflect the perspective of the quality function and may not represent the perspective of other functions or of executive management at the site or within the firm.

### Results

#### Respondents

A breakdown by product type of the total number of registered sites notified of the availability of the survey was 15 allergenic sites, 33 fractionated plasma protein (including recombinant analogs) sites, 63 therapeutics (including in-vivo diagnostics) sites, 30 in-vitro diagnostics (including blood grouping reagents) sites, and 22 vaccine sites. A summary of the responses by industry product type that were included in the survey results is shown in Table I.

Questions 1 through 4 pertain to firm and manufacturing site information. An analysis of the responses received by the industry follows each question.

#### **1. Your firm may make more than one type of product. For what type(s) of biological products at this site are you answering this survey?**

There were a total of 44 responses from 42 respondents received for this question.

**TABLE I**  
**Survey Respondent Information by Product Type**

Industry Product Type	Number of Responses*	Percent of Total Responses	Response Rate (%) per Industry
Vaccines	4	9	18 (4/22)
Fractionated Plasma Proteins	12	27	36 (12/33)
Allergenics	3	7	20 (3/15)
Therapeutics	20	45	32 (20/63)
In Vitro Diagnostics	5	11	17 (5/30)

\* Two of the 42 survey respondents indicated that two different types of products were manufactured at the site; therefore, the total number of actual surveys included is 42 and not 44.

- The greatest total number of responses was received from the therapeutics industry, with 20 registered sites submitting a response to the survey (representing 45% of the total responses received and a 32% response rate for the therapeutic products registered sites).
- The fractionated plasma industry was the most responsive of the five product types to this survey with a response rate of 36%.
- The least number of responses overall were submitted by the allergenic industry representing 7% of the total respondents.
- The In Vitro Diagnostics (IVD) industry had the lowest participation by product type in this survey with only 17% of registered sites responding.

**2. How many years has your site manufactured commercial biological products, 0–1 year, 1–3 years, 3–5 years, or >5 years?**

The majority of the respondents (39/42) have been manufacturing commercial biological products for more than 5 years. This includes all vaccine, allergenic, and IVD firms, all but one therapeutic firm, and all but two fractionated plasma protein firms that responded to the survey. No firms that have manufactured biological products for less than 1 year responded to the survey.

**3a. How many Team Biologics inspections were conducted at your site between November 2002 and November 2005?**

A total of 81 inspections were conducted by Team Biologics at respondent manufacturing sites. The ma-

jority of the industry respondents had at least two inspections within the 3-year period (November 2002 through November 2005). One vaccine facility had six inspections in 3 years, and two fractionated plasma facilities had four or five inspections in the 3-year period. These 81 inspections represent 38% of the total 212 inspections conducted by Team Biologics during this timeframe.

**3b. How many of these inspections resulted in the issuance of a Form FDA 483?**

Of the 81 inspections conducted at these sites, 66 (81%) resulted in issuance of a Form FDA 483 (483). This percentage is similar to the FDA records that show 90% of Team Biologics inspections resulted in issuance of 483s during this time period. The 66 483s issued to the respondents represent 34% of the total 483s issued. Also of note, of the sites that did not receive a 483, four sites were inspected twice since November 2002 (one manufacturer of allergenic products and three of therapeutic products).

**4. When was the most recent Team Biologics inspection of this site?**

Table II details the timing of inspections per product type for the survey respondents.

Analysis and results for Questions 5 through 29 pertain to industry feedback on general inspection practices, inspection focus, actions taken by the firm based on inspectional findings, compliance follow-up, and overall interactions of Team Biologics with the industry.

**TABLE II**  
**Team Biologics Inspection Timing per Product Type**

Timing of Most Recent Inspection	Number of Manufacturing Sites (by product type)					Percent by Inspection Timing
	Vaccines	Fractionated Plasma Proteins	Allergenic	Therapeutics	IVDs	
0–3 months	2	3	1	2	1	20%
3–9 months	1	3	0	4	1	20%
9–18 months	1	2	1	7	1	28%
18–36 months	0	4	1	7	2	32%
Total # of respondents	4	12	3	20	5	100%

**TABLE III**  
**Overall Summary of Operations/Procedures per Industry**

Operations/Procedures	Percent of Sites that Made Changes (by Industry)					Total Percent Across Industry
	Vaccines	Fractionated Plasma Proteins	Allergenic	IVDs	Therapeutics	
Priorities	25	40	33	40	44	42
Training	100	30	67	40	31	44
Design Control	25	10	0	0	13	11
Quality Unit Activities	25	20	100	0	50	39
Analytical Method Validation	0	20	33	0	6	11
Failure Investigation	100	60	33	80	56	67
Auditing	0	0	0	0	19	9
Process Validation	50	50	33	40	31	44
Specifications/Control Limits	25	50	33	40	38	42
Manufacturing Process Procedures	0	40	0	40	56	42
Product Distribution/Shipping	25	20	33	20	19	33
Sample Management	0	0	0	0	13	6
Written Procedures (record, document, change control)	25	60	100	40	69	61
Equipment Qualification	25	20	0	20	13	20
Equipment Upgrades/Changes	0	20	33	20	25	31
Facility Upgrade	50	10	33	0	13	17
Maintenance and Calibration Practices	0	20	0	20	13	13

**5. Did the most recent Team Biologics inspection result in modifications to any of the following operations/procedures at your facility?**

The overall analysis of operations and procedures that were changed as a result of the most recent Team Biologics Inspection are summarized in Table III.

The respondents from the vaccine industry (4) indicated that the all sites made changes after their Team Biologics inspections to training and failure investigation (100%).

Respondents (10) from the fractioned plasma protein industry noted that failure investigations and process validation were the primary focus of change after inspections by Team Biologics.

The respondents (3) in the allergenic industry indicated changes to quality unit activities and written procedures (document, record, and change controls) for all three firms that responded to the survey.

The respondents (16) in the therapeutic and/or in-vivo diagnostic industry noted changes to quality unit activities (50%) and failure investigation in (56%), with the most focus (69%) on written procedures pertaining to record, document, and change controls.

The respondents (5) in the IVD industry indicated changes to failure investigation procedures in 80% of the firms that responded to the survey.

Across the industry, of the sites making modifications due to the Team Biologics inspections, 67% reported changes to failure investigations, and this seemed to be a primary focus in most sites surveyed. Seventy-two percent (26/36) reported changes to production and process controls and 61% (22/36) for written procedures. Other changes reported overall were management of priorities, training, and quality unit activities (each at 39%, 14/36).

**6. Did the Team Biologics inspection focus on the more problematic areas of your operations versus areas that are operating in compliance?**

Sixty-three percent of the respondents (24/38) indicated that the inspection focused on the more problematic operations. The number of inspections that a firm received and the length of time since the last inspection did not appear to affect the responses.

**7. In your opinion, did the Team Biologics inspection focus on less important or trivial issues?**

Seventy-four percent of the (28/38) respondents indicated that the inspection *did not* focus on trivial issues. The industry breakdown of the remaining 26% that felt the inspection focused on less important issues was as follows: 1/3 for vaccines; 3/11 for fractionated plasma proteins; 0/3 for allergenics; 4/18 for therapeutics; 3/5 for IVDs. These responses are consistent with the responses in Question 6 and suggest that most inspections are reported to focus on areas of most importance to maintain compliance. There were also several comments by the respondents to this question, and some are included below:

- “While the focus may not have been on trivial issues, there were observations that could be classified as less important.”
- “For the most part it appeared that the issues that were discussed with the most fervor (from the inspector’s standpoint) were very minor and stemmed from a lack of understanding of the manufacturing process.”
- “Inspectors were not familiar or did not apply the concept of risk based approach and process understanding. Partly they followed a bureaucratic and formal approach.”

**8. Did the inspection identify any problem not previously identified internally?**

Of the 38 total respondents to this question, 42% indicated that compliance issues not previously recognized by the company were identified during the Team Biologics inspection. This includes 100% of the allergenics manufacturers, 80% of the IVD manufacturers, 36% of the fractionated plasma protein manufacturers, and 28% of therapeutic manufacturers. None of the vaccine manufacturers indicated that the inspection identified any problems not previously found internally.

**9. Did your corporation implement corrective actions at other sites (globally) based on this Team Biologics inspection?**

Fifty-six percent of respondents (15/27) with multiple sites indicated that corrective actions were implemented globally at other manufacturing sites after the

Team Biologics inspections. The data from this question are difficult to interpret for the 44 percent that responded “no”. Possible reasons could be that the firm may not have global systems in place, the observation may have been specific to a single site, or manufacturers may not have realized that corrective actions to observations should be applied across sites.

**10. Did your firm redirect prioritization within the quality system?**

Almost half (46%) of the respondents reported a redirection of priorities within their quality systems subsequent to FDA inspections. This is consistent with the responses of Question #5, where many firms reported changes to priorities (40%), changes to other aspects of the quality system such as failure investigations and written procedures (64% for each), as well as quality unit activities and training (39% for each).

**11. Did you make substantive changes to the approach or procedures for investigating failures as a result of the FDA 483?**

Seventy-three percent of respondents did not make changes to approach or procedures for failure investigations as a result of the 483; 11% of these respondents indicated that this question was not applicable (possibly because these firms did not receive a 483 observation). Twenty-seven percent of all respondents indicated that substantive changes to failure investigation were made as a result of the 483, the highest of which came from the therapeutic industry (6 out of 15 firms that received a 483 observation).

**12. Did the inspection identify the lack of any procedures?**

Nineteen percent of the respondents indicated that the Team Biologic inspections identified the lack of required procedures, with IVD manufacturers at 50% (2/4).

**13. Did a system/process that was previously validated require revalidation?**

Overall, 49% of respondents indicated that revalidation was necessary as a result of findings in Team Biologic inspections. This includes 100% (3/3) of vaccine manufacturers, 50% of IVD manufacturers (2/4), 64% of fractionated plasma protein manufacturers (7/11), 39% of therapeutic manufacturers (7/18), and 33% of allergenic manufacturers (1/3). It is

difficult to draw clear conclusions; however, the higher percentages in the vaccine, IVD, and fractionated plasma protein industries may be attributed to the maturity of the industry where processes needed to be revalidated to meet current regulatory expectations.

**14. Did the inspection identify any systems or processes that had not yet been validated?**

Identification of systems or processes requiring validation (i.e., not revalidation) during the inspection occurred for 32% of all respondents (12/37). Breakdown by product type was as follows: 75% IVD (3/4), 66% vaccine (2/3), 45% fractionated plasma protein (5/11), 33% allergenic (1/3), and 11% therapeutic (2/18). As with Question 13, these results may be attributed to the maturity of certain industries, where processes and systems not previously validated needed to become compliant with current regulatory expectations.

**15. Did your site make overall changes to your current validation approach as a result of the inspection?**

Twenty-seven percent of the respondents (10/37) indicated that changes in current validation approach were made as a result of the Team Biologics inspections. All of the vaccine and allergenic manufacturers responded “no” to this question, which was not consistent with Question #5 where vaccine and allergenic manufacturers indicated changes were made to operations/procedures for process validation after the inspection. Perhaps changes may have been made with respect to procedures but not to the overall validation approach. The breakdown for the remaining industries that made changes to validation approach was as follows: 64% of fractionated plasma protein (7/11), 50% of IVD (2/4), and 11% of therapeutic manufacturers (2/18).

**16. As a result of the most recent Team Biologics Inspection, were there any chemistry, manufacturing, and controls (CMC) changes that warranted any of the following submissions to the Agency?**

Overall, 26% of respondents (9/34) indicated that regulatory filings were submitted as a result of the most recent Team Biologics inspection. One firm submitted two filings, consisting of one annual report and one Changes Being Effected (CBE) filing. It is difficult to draw clear conclusions as to why submissions were filed,

**TABLE IV**  
**Summary of CMC Submissions**

Submission Type	Number Submitted	Overall Percentage of Respondents
Annual Report	7	21%
Changes Being Effectuated (CBE)	2	6%
CBE-30	1	3%
Prior Approval Supplement (PAS)	0	0%

whether there was a failure to file in accordance with regulatory requirements or if the regulatory submissions were required due to a remediation activity as a result of the inspection. Results are depicted in Table IV.

The respondents from the Allergenic (3) and IVD (3) industries indicated that no regulatory filings needed to be submitted as a result of findings in the Team Biologics inspections.

**17. In general, but as a result of the Team Biologics inspection, have you increased the number of submissions to the FDA (PAS, CBE, or CBE-30 supplements) because of greater awareness that such submissions are required?**

Overall, 13% of respondents (5/38) indicated an increase in submissions due to greater awareness after the Team Biologics inspection. The specific industries that increased the number of submissions were the fractionated plasma protein (36%, 4/11) and IVD (20%, 1/5) industries. The fractionated plasma protein respondents appeared to be the most affected by under-reporting of changes.

**18. Did you make staffing changes to senior management, quality control, quality assurance, or manufacturing departments?**

Staffing changes were made for one respondent each in the allergenics, IVD, and vaccine industries, and two respondents in the therapeutic industries. The majority of changes were increases to staff. However, the staffing change indicated by the IVD respondent was a replacement of senior management.

**19. Was product recalled, quarantined, or distribution disrupted?**

There was one instance of recall, quarantine, or disruption or distribution from a therapeutic protein manufacturing site.

**20. Did the last Team Biologics inspection help you better understand any of the following?**

The categories for this response and the results are presented in Figure 1. For the majority of respondents (70%), the inspection helped with the firm's understanding of the FDA's expectations on CGMPs. Eleven percent of respondents indicated that there was a better understanding of FDA guidances and initiatives after the inspection. Seven percent of respondents indicated a better understanding of statutes and regulations, while no respondents indicated that the inspection helped with understanding ICH guidances. Therefore, inspections appear to help improve a firm's understanding of the agency's expectations, especially CGMPs.

**21. Due to the last Team Biologics inspection, has your firm spent proportionally more, less, or no change in the money/resources for the following categories?**

The resource categories for this response and the results are presented in Figure 2. There were a total of 36 respondents to this question regarding changes due specifically to the last inspection. The category with the largest increase in resources/money due to the last Team Biologics inspection was in the development of procedures (33%), followed by facility upgrades at 23%. One firm (therapeutic) spent less on training as a result of the last inspection. Only 9% (3/36) acknowledged an increase in spending on automated systems (software/hardware), two of which had inspections 18–36 months ago.

**22. Due to the Team Biologics Inspection Program as a whole, has your firm spent proportionally more, less, or no change in the money/resources for the following categories?**

The responses indicated that across all industries, more money and resources were dedicated to training (56%), development of procedures (56%), and facility upgrades (46%). These results appear to be consistent with the responses to Questions 5 and 21. Only 3% of

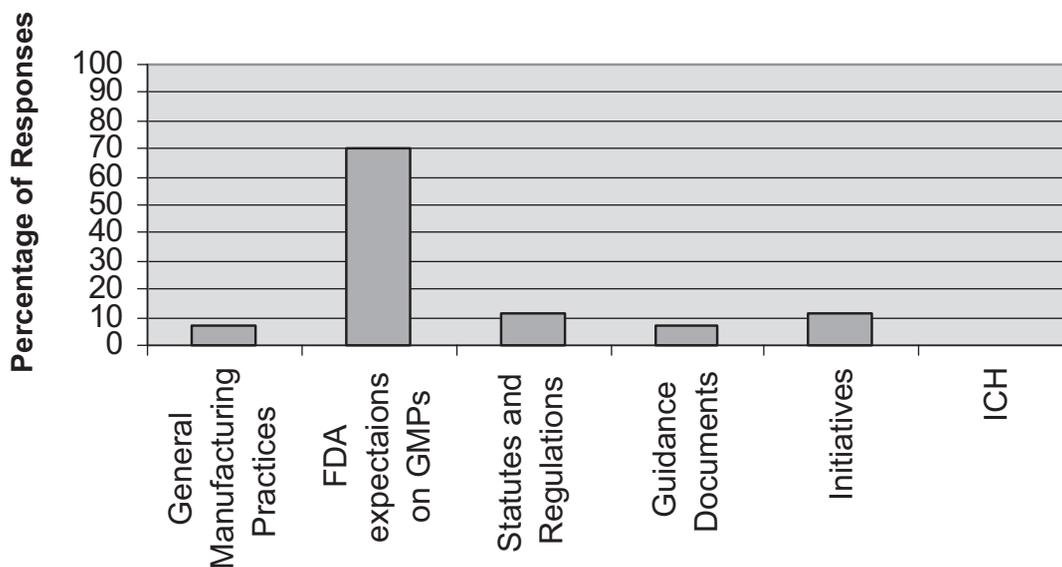


Figure 1

**Areas of Better Understanding Post Inspection. ICH = International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)**

the responders identified that less money/resources has been spent on any of the seven specified areas.

Representative comments from these respondents are listed below:

**23. Overall, has the Team Biologics Program had an impact (positive, negative, or neutral) on your operation? (e.g., regulatory, reputation, business, operations, culture of quality).**

- “Positive. The team that recently inspected us was experienced, thorough, tough, but also fair. They had been to our facility two years ago, so we knew what to expect and spent a good deal of time and effort preparing for what we considered to be a successful inspection. The preparation resulted in an overall higher level of quality than would have

The majority (68%) of respondents indicated that the Team Biologics inspections had a positive impact.

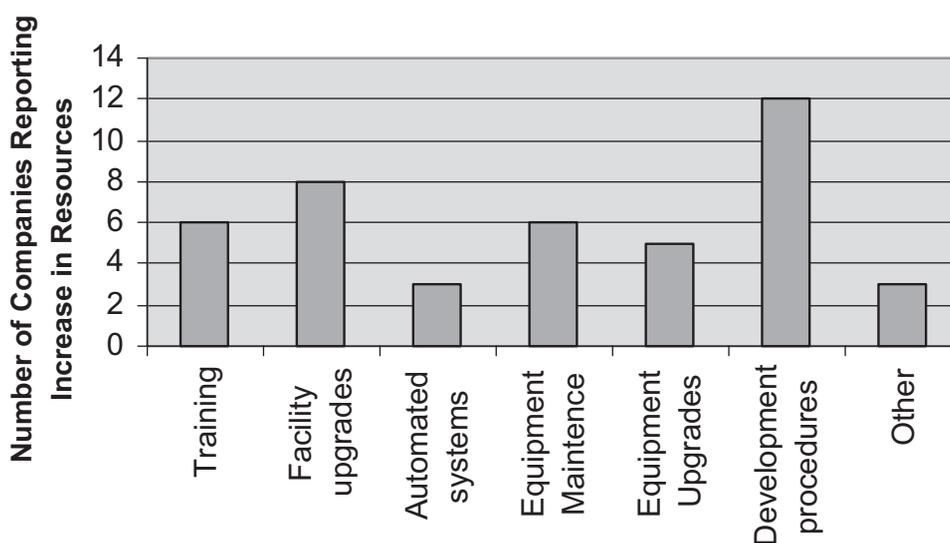


Figure 2

**Money/Resource Allocation**

been achieved had we not known that Team Biologics would be there.”

- “The program has required a culture of quality that would not have been present without the expectation of inspections, 483s, and other actions by the program. Management would not have put quality into operations/products unless required by the FDA. The program has required management to listen to Quality and to put a higher priority on Quality’s requests.”
- “Positive; with continuous improvement as a result. We do expect a more risk based approach in the future, based on implementation of ICH 8 and 9.”

Other positive impacts were noted as improvement in understanding regulations and CGMP (correlates with responses to Question 20), improvements in communication and alignment between quality and operations departments within a firm due to involvement in the inspection, and confirming to senior management the validity of quality department focus.

Thirteen percent of respondents (4/31) indicated that the program had a negative affect on the firm’s operation. Representative comments from these respondents included

- “With each inspection, the company gets a better insight into the current initiatives and focus from Team Biologics. However, during the most recent inspection, the method used by the investigator required significant manipulation of our quality data metric to present in a specific format. This was time consuming and disruptive to normal operations. Data in our current format could be easily reviewed and assessed for compliance.”
- “Would like to see FDA provide more education for companies and more clear regulations. Providing a citation, then education/interpretation seems like the wrong approach.”
- “Positive and negative. In a positive sense we are more compliance orientated; however, sometimes good science has suffered because of compliance.”

Nineteen percent of respondents indicated a “neutral” impact. Only one written comment was received that

stated the quality of inspections has varied, but the most recent inspection drove positive change and clearly identified issues and FDA expectations.

#### **24. If you had interactions with FDA compliance officials after the inspection, was the interaction helpful in clarifying issues and understanding FDA’s expectations?**

There were a total of 36 respondents to this question. Of these 36 respondents, 44% (16/36) responded that this question is “not applicable”. Of the remaining 20 respondents, 18 respondents indicated that interactions with FDA after the inspection were helpful. Specific comments include the following:

- “FDA compliance officials have generally been supportive in our efforts to clarify controversial issues that were not resolved during the inspection.”
- “Discussions regarding a particular 483 clarified the situation.”
- “Very productive and helpful in understanding expectations and partnering with FDA”
- “Presentation was provided to FDA after the inspection because of the concern in the way certain observations were worded. However, a larger FDA audience clarified that we were on the right path and doing what we needed to do—even though the inspector had worded the observation more harshly and we thought it might lead to a warning letter.”
- “Team Biologics investigator was attempting to collect evidence after closeout of the inspection. Compliance officials stepped in and resolved the issue.”

Two of the respondents indicated that the compliance officials were not helpful in clarifying issues after the inspection. Other negative comments to this question included

- “Disconnects between team Biologics and CBER required additional communication post inspection.”
- “[Establishment Inspection Reports (EIRs)] are not received in a timely manner”

**25. Do you think the post-inspection correspondence from compliance officials focused on the appropriate issues?**

Out of the 36 respondents, 28% indicated that this question was applicable. Of those 14 respondents, only two respondents indicated that the focus of the post-inspection correspondence was not on the appropriate issues. Written comments were received and are summarized below:

- “While our company has not had to have any significant discussions, the brief correspondence we have had seemed adequate and seemed to reflect an understanding of the issues.”
- “No correspondence received from FDA. We sent our original 483 response and a progress update to FDA, so far, both without comment.”
- “The EIR is an important document to specify the issues.”

**26. In your opinion, was the assessment of your operation conducted fairly?**

Of the 34 respondents, 88% indicated that the Team Biologics inspections were conducted fairly. The comments received included:

- “The team that was sent to us was excellent.”
- “The inspector was respectful, considerate, and allowed time for review and collection of materials. Very straight forward approach.”
- “With the usual exceptions for specific issues of misunderstanding, Team Bio inspections have generally been fair.”

The other 12% of respondents indicated that the inspection was not conducted fairly, and comments include the following:

- “One inspector was very fair, another was not.”
- “The EIR transported a different message than the closing meeting and the FDA 483.”
- “One investigator was neither familiar with applicable guidelines for inspection of biopharmaceutical API manufacturing (e.g., Q7A) nor familiar

with biopharmaceutical processes (e.g., column chromatography).”

**27. Does your firm feel there are clear and adequate processes for discussion and dialog of inspection issues with inspectors and/or compliance officials?**

This question elicited a total of 28 comments. Over half indicated that there was adequate discussion and dialog of inspection issues with investigators and compliance officials. The following are actual comments received and are representative of all 16 responses:

- “FDA is prepared to listen when we challenge observations. In some cases it prevented a 483.”
- “Very willing to discuss and clarify differences in opinion and assist in coming to a satisfactory conclusion.”
- “There was ample time during the inspection to discuss issues. In many cases our explanations averted 483 observations. The few comments we did receive were generally valid.”
- “Inspectors clearly explained their perspective.”
- “Dialog during and after the inspection was open and collaborative.”

One comment was specific to the IVD industry:

- “In our experience, there have been sufficient channels by which difficult issues could be discussed and resolved. . . . There does need to be continued effort to encourage inspectors to gauge their inspectional observations based on risk to the final IVD product (for IVD manufacturers). . . . but certainly there needs to be a real effort to consider risk and other key considerations before forcing IVD manufacturers to implement the same levels of controls as injectable/vaccine manufacturers.”

Two respondents noted that the opportunities to have open discussions with the investigators during the inspection have improved over time. One respondent indicated that while generally discussion/dialog of inspection issues was adequate, it appeared the center seemed pressed for time and resources.

Approximately 35% (10/28) of the comments indicated that there are not adequate processes for discus-

**TABLE V**  
**Areas of Suggested Improvements to the Team Biologics Program**

Comments	Percent of Total Responding
More technically supported inspections	28%
No change to the program	18%
Risk based/quality systems approach to inspections	14%
More training for investigators	14%
More consistency and uniformity	7%
ICH guideline-based approach to inspections	7%
More timely receipt of the EIR	4%
Clear and easy anonymous feedback options	4%
Pre-inspection notification	4%

sion and dialog of inspection issues. The following are actual comments received and are representative of all 10 responses:

- “The biggest issue we have with the Team Biologics program is the inconsistency between investigators. Different investigators will focus on different issues. This can lead to focus on areas not critical to the product line (e.g., environmental controls for a non-sterile product). The focus of the investigator is not open for discussion based on our experience.”
- “We feel we can discuss but I do not feel there are clear procedures.”
- “It appears that the FDA is inflexible often and compliance with their wishes is the only way to remain in business. When we have challenged them, the results were negative, sending us a clear message that they only want our obedience.”
- “No, because each investigator even on the same team [has] different approaches for discussion and dialog. Time after inspection before issuance of the EIR is long and there is no indication in the interim if the 483 response is satisfactory.”
- “No, depends on the investigator. Inspectors are often not open to accept explanations. As inspectors are not experts in every field it is problematic if processes are not understood. Company culture often tends to accept observations and do changes even if it felt that they are incorrect or not necessary. Companies do not use the opportunities of programs such as the Dispute Resolution Program.”

- “Inspection observations tend to be more based on individual inspector’s opinions rather than Agency expectation or industry standards. Discussion with inspectors is also very much dependent on their personality. There is no evidence that center policies reach the inspectors in a timely manner (e.g., risk assessments and management).”

**28. Please provide suggestions/comments for improvements to the Team Biologics Program.**

A total of 28 suggestions and comments were submitted; Table V summarizes the results.

**29. Was this questionnaire straightforward to complete?**

Ninety-two percent of the respondents answering this question (32/35) indicated that the survey questionnaire was straightforward to complete. Only a few written comments were provided, but they could help in constructing and issuing similar surveys in the future. One comment received stated more choices other than “yes” or “no” should be offered. The project team tried to create questions and response options to be balanced between simplicity of responding and gathering enough information for the team to make valid conclusions (with limitations on the number of complicated questions and on the number of variables for analysis). After reviewing the responses, the team agreed that more choices on some questions could have obtained more specificity in helping to draw conclusions. One comment suggested offering the survey in alternate languages (other than English). The team did consider making the survey available in more than one language, but since the survey was issued to both U.S. FDA domestic and international firm

locations in a large number of countries, to be fully inclusive this would have required a dozen different languages to be offered. Therefore, English was ultimately chosen as the only language to most effectively utilize the team and PQRI resources.

## Conclusions

Prior to implementation of the agency's CGMP initiative, internal FDA work groups were formed to focus on several identified areas for improvement in the Team Biologics Program operations, including the implementation of a quality management system, standardization of training, and development of program evaluation metrics. This survey of the biologics industry was conducted to obtain input on the impact of the Team Biologics inspection program, specifically, to gain industry feedback on general inspection practices, inspection focus, actions taken by the firm resulting from inspections, compliance follow-up, and overall interactions of Team Biologics with the regulated industry. Through use of this information, the FDA's objective is to evaluate the Team Biologics Program and to implement any changes for enhancement of program performance.

In general, the survey respondents correlate well with the product-specific registered types within the biologic industry that are inspected by Team Biologics. While it is difficult to draw definitive conclusions from the data because of the limited numbers of responses from specific product types, there were relevant trends noted that perhaps will be useful to monitor over time.

The three areas most impacted by Team Biologic inspections were "Production and Process Controls", "Failure Investigations", and "Facility/Equipment Controls" with changes being reported in Question 5 as 72%, 64%, and 53%, respectively. With the Team Biologics system approach to inspections and the focus on deviations/failures, it is no surprise that changes to these areas were implemented as a result of the inspections.

In review of data for questions 22, 23, 24, 27, and 28, which asked for the sites' assessment of the Team Biologics program, responses were generally positive, with 68% stating that the program had a positive impact on the sites' operations and 88% assessed the Team Biologic inspections as being conducted fairly. Specific positive comments noted the willingness of the FDA to discuss and clarify differences and the opportunity for open dialog and discussion. Negative comments empha-

sized different investigator approaches for discussion and dialog and inconsistency among investigators.

The survey also solicited suggested improvement to the Team Biologics program. Eighteen percent felt that no changes were needed. The remaining responses identified investigator training and consistency issues, more technical support of inspections, and better alignment with the new risk-based CGMP approach.

Since the respondents were asked to focus responses to the questions on the most recent Team Biologics inspection, it is difficult to analyze the impact of the Team Biologics experience over time. Periodic surveys of the same or similar questions would allow changes to be seen over the baseline created by this questionnaire.

In summary, data and written feedback were obtained regarding industry interactions and experiences of Team Biologics inspections at various product facilities over the past 3 years. It is believed that the information presented and conclusions drawn will be useful to those companies currently manufacturing licensed biologic products, as well as those manufacturing biologic products at the pre-licensure phase and anticipating Team Biologics inspections in the near future. In addition, some of the suggestions from feedback obtained through this survey, for both inspections and compliance aspects of Team Biologics program operations, could perhaps be incorporated in the abovementioned areas identified for improvement by the FDA, and they may prove useful to the agency in its overall effort to streamline the inspection process.

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