December 29th, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA–2014–N–1575: Best Practices for Communication Between the Food and Drug Administration and Investigational New Drug Sponsors During Drug Development; Request for Comments

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on "Best Practices for Communication Between the Food and Drug Administration and Investigational New Drug Sponsors During Drug Development." This docket represents an important step in identifying effective practices for communication during drug development, both through official meetings and less formal means of communication outside of established meetings. Modern drug development requires scientific collaboration by all parties in the innovation ecosystem, and promoting effective FDA-Sponsor communication is fundamental to our ability to translate scientific discoveries into safe and effective new therapies for patients.

BIO represents nearly 1,000 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture and a cleaner and safer environment.

I. INTRODUCTION:

BIO strongly supports the Prescription Drug User Fee Act (PDUFA 5) program to enhance FDA-Sponsor communication, which is based on FDA's stated philosophy that "timely interactive communication with Sponsors during drug development is a core activity to help achieve our mission to facilitate the conduct of efficient and effective drug development programs, which can enhance public health by making new safe and effective drugs available to the American public in a timely manner." In recent public statements, FDA has noted that "Sponsors who avail themselves of the opportunity to meet with FDA early in development have substantially reduced the time from the start of human testing—when FDA first becomes involved—until

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marketing approval."[1] For instance, companies that meet early with FDA have experienced a median product development time reduction of 1.4 years and upwards of 2.1 years for orphan drugs. Thus, increased communication during drug development ultimately will reduce time to market and speed the availability of important new therapies to patients.

There are currently a number of formal avenues for FDA-Sponsor communication. For example, current regulations (21 CFR 312.41(b)) require FDA to provide consultative advice during the investigational new drug (IND) phase.[2] There are also existing Good Review Management Practices (GRMPs) that encourage communication with the Sponsor during the IND phase, as well as PDUFA mechanisms that allow for these communications (*e.g.,* Type A, B, and C meetings and the Special Protocol Assessment (SPA) process).[3] Sponsors are encouraged to take advantage of milestone meetings utilizing these established meetings procedures.

Changes to a development program often need to be discussed and addressed by the Agency in a more expeditious fashion to help prevent or minimize delays in development and for the Agency to be perceived as a collaborator in drug development. Many of these time-sensitive communications can occur efficiently outside of formal meetings. While some Review Divisions should be commended for providing advice and working in a responsive and collaborative way, this is not the norm in all divisions. BIO members have noted that communications practices can be inconsistent both within and across Review Divisions.

Additionally, early communications on development do not always represent the entire Agency's recommendations. For example, early communications for combination products from the Center for Drug Evaluation and Research (CDER) do not always include input from the Center for Devices and Radiological Health (CDRH), though such input could inform development programs.

BIO's expectation is that the results of this docket will inform forthcoming FDA guidance on best practices for FDA-Sponsor interactions during drug development (expected in FY15), and to encourage greater timeliness, quality and consistency in communication across and within FDA Review Divisions through routine staff training and standard operating procedures.

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[1] FDA, Woodcock, Janet, Testimony before the House Energy and Commerce Committee, "21st Century Cures: Modernizing Clinical Trials and Incorporating Patient Perspective" (July 11, 2014) "For the 181 new drugs approved from 2008 - 2013 (for which a clinical development time could be calculated), the Sponsors of the 67 applications who met with FDA before submitting their Investigational New Drug (IND) applications had a median development time of only 6.6 years, compared to 8.0 years for applications for which such a meeting did not occur (a mean reduction of 1.4 years). The median drug development time for applications for which a meeting with FDA was held at the end of the Phase 1 (EOP1) milestone was 1.1 years shorter than for applications for which an EOP1 meeting did not take place. For orphan drugs, drug development was a median of 2.1 years shorter."

[2] (21 CFR 312.41(b)) "On the Sponsor's request, FDA will provide advice on specific matters relating to an IND. Examples of such advice may include advice on the adequacy of technical data to support an investigational plan, on the design of a clinical trial, and on whether proposed investigations are likely to produce the data and information that is needed to meet requirements for a marketing application."

[3] *Good Review Practice: Good Review Management Principles and Practices for Effective IND Development and Review.* http://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/manualofpoliciesprocedures/ucm349907.pdf

II. BIO SURVEY ON EFFECTIVE FDA-SPONSOR COMMUNICATIONS

In support of the PDUFA V Enhanced Communications program, BIO initiated a multi-year survey initiative to better understand biotechnology company experiences during drug development and to identify best practices for FDA-Sponsor communication. The online survey was administered by a professional survey firm, Penn Schoen Berland (PSB), between June 18 and September 14, 2013 and received 102 unique responses from 91 BIO member companies. A preliminary analysis of the results is included in the slide deck prepared by PSB, which can be found in the appendix of these comments.

As discussed below, the initial survey demonstrated moderate improvement in certain communication practices in recent years, however, 40% of respondents reported that some FDA-Sponsor miscommunication contributed to one or more delays in product development.

BIO launched the second phase of this initiative in the summer of 2014. This phase includes collecting information on FDA and Sponsor interactions during drug development for over 190 individual clinical programs currently under development. PSB will complete the initial analysis in January 2015 and we look forward to sharing the results with FDA.

The 2013 survey demonstrated wide variability in the level of satisfaction in communication across different Review Divisions. Those divisions that communicated reasonably well did so across most avenues of communication—formal meetings, written letters, and informal communication—while those that were ranked lower communicated less effectively across all of those channels. BIO would like to partner with the Agency to identify the best practices from those divisions with the highest levels of satisfaction so that FDA can apply those practices to the other divisions to improve overall consistency.

Key Points:

- 70% of respondents were generally satisfied with the state of FDA-Sponsor communication, up from 64% in the early stages of PDUFA 4.

- However, only 18% of Biologics License Applications (BLA) Sponsors found the quality of communication to be very good or excellent, compared to 35% of New Molecular Entities (NMEs). The quality of communication was deemed best for Breakthrough Therapy-designated products (52%) and Priority Review products (52%).

- Of the respondents reporting that FDA-Sponsor miscommunication contributed to one or more delays in product development, 44% of these delays were caused by an unexpected FDA reinterpretation of an existing agency policy.

- 78% of Special Protocol Assessments required multiple review cycles.

- Survey respondents reported wide variability in communication across different Review Divisions; Figure 1 shows the divisions that ranked highest and lowest for communication satisfaction. Figure 2 evaluates the level of

communication satisfaction across the Review Divisions with which BIO member companies most commonly interact.

Figure 1: Satisfaction with Communication Varies Among Review Divisions

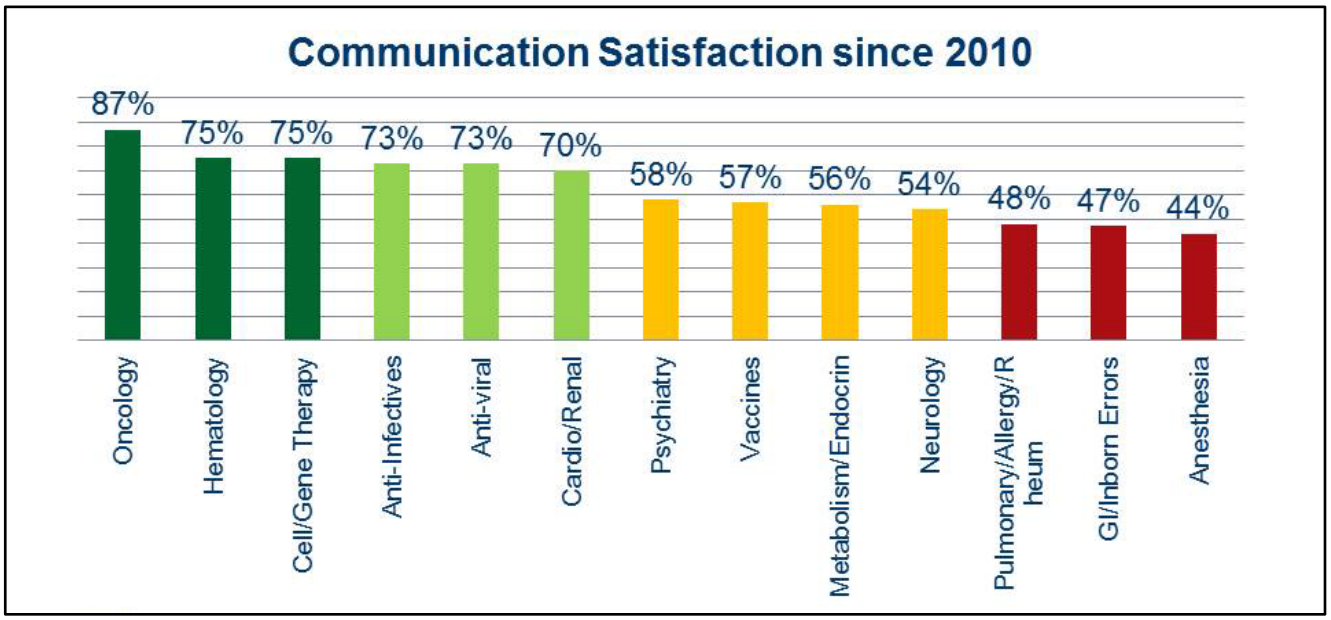
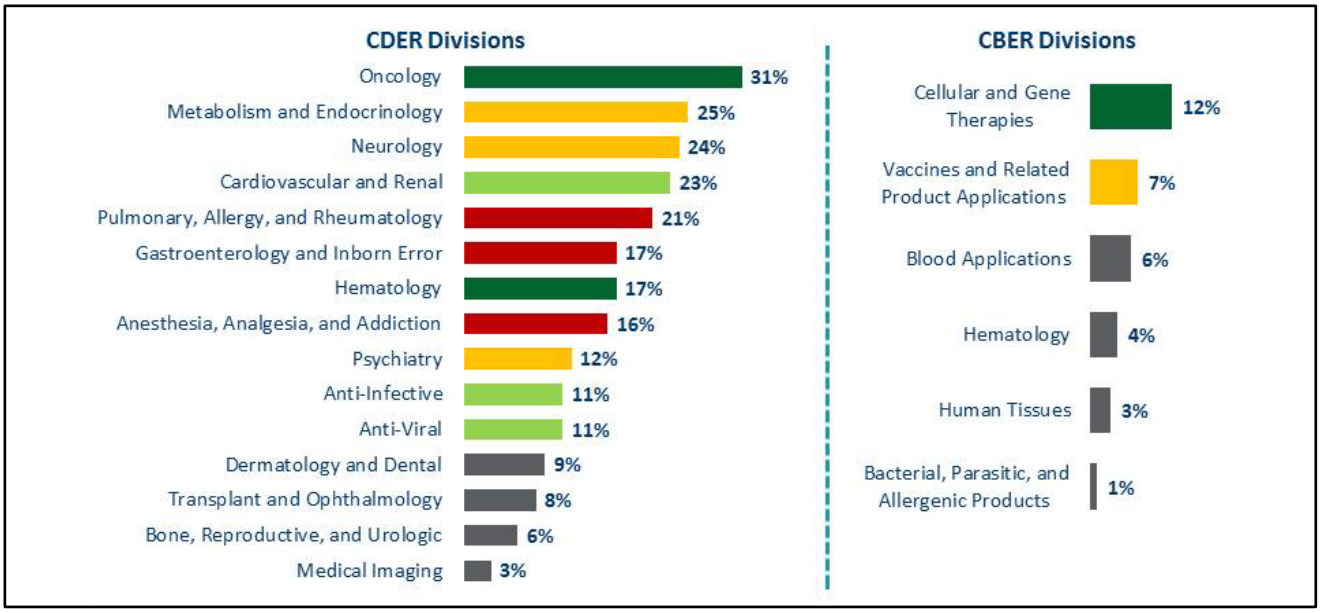


Figure 2: BIO Member Interactions with FDA by Review Division



III. IMPROVING SCIENTIFIC DIALOGUE AND ENABLING EFFECTIVE COMMUNICATION DURING DRUG DEVELOPMENT

Based on our survey and discussions with members, BIO identified four main areas where improvement in communications could enable a more effective development and review process:

A. Improving Scientific Dialogue
B. Improving Effectiveness of Formal Meetings with FDA
C. Improving Communications between FDA and Sponsors Regarding Emerging and Evolving Science
D. Improvements to Communication on FDA Website

Below we have noted several points for FDA to consider as it drafts guidance on this topic.

A. Improving Scientific Dialogue

Communications best practices should improve the ability for Sponsors and FDA to engage in scientific dialogue in a collaborative manner across all Review Divisions during drug development to ensure there is timely resolution of issues and prevent any unnecessary delays.

While there have been significant improvements in how FDA and Sponsors communicate during drug development over the past few years, there are still issues with consistent and transparent practices across Review Divisions. Given the resources needed to prepare for formal meetings, efficiencies for FDA and Sponsors could be gained if there were mechanisms for more frequent feedback from the Review Division outside of formal Type A, B and C meetings and consistency across Review Divisions. For example, under what circumstances is it more appropriate for a Sponsor to communicate with FDA via informal communications (email, telephone, etc…) and when should an issue be addressed through a formal PDUFA meeting? Additionally, we continue to note a lack of cohesive process for programs that involve multiple FDA Centers, specifically CDER and CDRH. We believe FDA's best practices guidance should address combination products and diagnostics to ensure that inter-Center communication and coordination are adequately addressed.

We recommend that any best practices training is structured for consistency across Review Divisions, but tailored to meet the specific needs of each Review Division. The training should provide both Sponsors and reviewers with examples of what types of issues could be addressed through informal communications.

Specifically, we would like any best practices guidance and training to address the following:

- Appropriateness of Types of Communication: FDA should clearly define the appropriate type of communication (*i.e.*, email, teleconference, IND submission of request for comment/advice, formal meeting request, etc.) to be used to address various categories of questions. In the case where it is determined that the answer being sought requires formal vetting and documentation by FDA or review of data, preliminary communications can help to prevent multiple meetings or letters to obtain the appropriate answer.

- Facilitating Timely and Interactive Communications via Teleconference: Many Review Divisions currently provide an opportunity for a brief teleconference with Sponsors to allow subject matter experts to discuss specific technical or time-sensitive issues, as needed. These teleconferences can be quickly scheduled, limited in scope and duration—for example for 15 or 30 minutes—to brief the Agency on time-critical issues, such as pre-approval use of a drug in development or safety-related issues. We recommend expanding this best practice across Review Divisions. The meeting request would include limited briefing information (*e.g.,* 5 slides or 7-10 pages). The teleconference would include a limited number of participants from FDA and the Sponsor and standard documentation would be shared afterwards with all participants. For important development questions requiring Agency input, where some live discussion would be useful toward gaining agreement, a shorter meeting format with quick scheduling could be useful (*e.g.,* addressing potential clinical hold questions or discussing data requirements for submission to support a new protocol under an existing IND). These types of interactions to help align on an issue more expeditiously could reduce the need for additional formal meeting requests or improve the efficiency of any follow-up meetings.

- Access to Agency Review Staff: BIO suggests establishing an Agency policy and process regarding scenarios where Sponsors may contact Agency staff (in addition to the Project Manager function). For certain issues that arise during development (*e.g.,* changes being considered in endpoint assessments), the Sponsor would benefit from direct access to Agency staff within a specific functional area (*e.g.,* Clinical, Chemistry, Manufacturing, and Controls (CMC)). Best practices should identify instances where direct communication with Agency staff may enhance speed with which questions and answers can be facilitated. Any guidance should address the type and frequency of communication that would allow FDA to receive questions, identify an answer and respond to the Sponsor. These processes should acknowledge the workload and time commitment that medical reviewers dedicate to the review of INDs, New Drug Applications (NDAs), and BLAs, and carefully balance that consideration with their capacity to respond to important IND-stage Sponsor inquiries.

- FDA Written Responses to Requests for Advice: Given the resources needed to prepare for Formal Meetings, efficiencies for FDA and Sponsors could be gained if there were a mechanism for more frequent written feedback from the review team outside of Formal Type A, B or C meetings, with consistency across Review Divisions. We suggest establishing target timing of 30-60 days from submission for request for advice (per 21 CFR 312.41) to respond to the Sponsor. Sponsors would benefit from having timely responses to requests for advice, as these requests are important to continuation of ongoing clinical programs but may not fall into a Type B meeting category. For example, requests for comments and feedback on study protocols outside of formal avenues are sometimes under review for extended periods of time. In this situation, it is difficult for the Sponsor to plan development timelines and budgets, to ensure that advice from other regulatory agencies will be aligned and coordinated with FDA comments, and to ensure that feedback from the Agency is implemented prior to study initiation. As current timelines for responding to requests for comments differ across Review Divisions, we encourage that any forthcoming guidance establish clear delineation of timelines for feedback. Other examples where timely feedback would be beneficial to the Sponsor and speed development times include function specific questions such as those for CMC or protocols related to

postmarketing requirements and commitments (PMRs/PMCs). The scope should also include requests for which the Review Division will need to request participation from other offices (*e.g.,* Study Endpoints and Labeling Development (SEALD) for patient-reported outcomes (PRO); CDRH for companion diagnostics and human factors protocols).

- Creation of Standardization and Templates for Routine Communications: We encourage standardization for written and telephone communication methods across Review Divisions. We acknowledge the need to send official correspondence via post; however, as paper correspondence may take several days to arrive, we encourage the adoption of standard processes across Review Divisions that allows for the sending of copies of official correspondence as a PDF or similar file type via secure email. Additionally, we recognize the value of telephone correspondence. Given that voicemails may not be heard in a timely manner, we suggest the further adoptions of a standard process across Review Divisions that allows for the use of secure email for informal correspondence. Use of templates for letters such as "study may proceed" would improve consistency (covering key categories of information including the annual reporting period). This can reduce the call/email volume to project managers (PMs) for routine information. FDA should also respond in the same manner in which the Sponsor communicated with them (*i.e.,* FDA should respond via email if the Sponsor initially communicated via email).

- Communication with Email Accounts: As a best practice, we suggest that Review Divisions should acknowledge receipt of Sponsors' emails within one business day. Additionally, response times for communication with general/blind FDA email accounts are widely variable. While some will acknowledge receipt of communications within 24 hours, others will take up to a week or more.

- Staff Assignments: In addition to assigning main contacts for each program, both the Agency and the Sponsor should assign alternates. The Agency and the Sponsor should provide updates as they become available. This should be extended to include Supervisory PM and Division Director information. Such a practice will provide clarity regarding key contacts and key personnel changes (*e.g.,* recent Division of Oncology Products 1 (DOP1) Division Director change) and help preserve continuity in the review when there is turnover during reviews.

- Improvements to the Enhanced Communications Office: The BIO survey found that while FDA has made the efforts to publicize the existence and availability of the Enhanced Communications Office, the office remains underutilized and often unknown to Sponsors. BIO would like to partner with the Agency to continue to raise awareness of the Enhanced Communication Office as a resource for Sponsors, for example through webinars or conferences.

B. Improving Effectiveness of Formal Meetings with FDA

Sponsors often do not take advantage of entitled meetings with FDA either due to perception that the value of these meetings is not high enough to allocate the resources and time required to participate in such meetings or a perception that any such conversations may lead to a higher regulatory burden than Sponsors would have otherwise. Best practices should provide information about how such discussions before, during and after would be valuable to Sponsors and serve to

identify and resolve key issues in the most effective manner possible. Below we provide a few specific examples of such improvements for your consideration.

General Considerations:

- Understanding "Regulatory Speak": We request that FDA provide guidance and training that better clarifies—to both Sponsors and reviewers—how the Agency should communicate to Sponsors the limitations of what the Agency can or cannot say in the context of a regulatory communication and how the Sponsor should interpret the type of "regulatory speak." For example, as a regulatory agency, FDA can provide guidance on acceptable and validated scientific methods, but the Agency cannot compel a Sponsor to take one approach to drug development over another. Based on the Agency's past experience and perspectives across many confidential drug development programs, FDA may use terms such as "encourages," "cautions," or "advises" in a meeting to provide guidance to a Sponsor. In some instances, a Sponsor may not interpret FDA's feedback as definitive or absolute and may continue a particular approach to drug development at risk, which can create issues at later stages of development or review. Consequently, Sponsors should recognize the weight and significance of these terms used by FDA in formal meetings and appreciate the limitations of what the Agency can communicate. An upfront understanding of the vocabulary that is used in regulatory communications, such as through a disclaimer at the start of each meeting or in the meeting minutes and utilization of these terms in in a more consistent manner would serve to minimize miscommunications between FDA and Sponsors. Additionally, consistency between spoken and written feedback is encouraged.

- Preliminary Comments: We understand that FDA typically aims to send written preliminary comments at least 48 hours in advance of a formal meeting, which should be viewed as a best practice in order for a productive meeting to occur. If the FDA is requesting a response from the Sponsor, the preliminary comments should be provided four business days prior to the meeting. In the experience of BIO's members, there has been a trend for the Agency provide these preliminary comments very late (within 24 hours of the meeting or less); occasionally, comments are only received at the meeting, and are thus not "preliminary" at all. Providing comments so close to the scheduled meeting makes it very difficult for Sponsors to determine if a meeting should still be held (or changed to a teleconference) and it may have a considerable impact on travel plans. If the Sponsor decides to proceed with the meeting, it can be quite challenging to adequately prepare verbal or written responses if FDA's comments are significant or FDA provided preliminary comments on matters beyond the scope of questions posed in the Briefing Document. Where comments are received only at the time of the meeting, it is difficult if not impossible for the Sponsor to respond substantively to any of the issues raised in those comments; however, by such point, the responses and time to prepare for and attend the meeting have already been expended.

Pre-IND and IND Meetings:

- Pre-IND Meetings: We have seen an increased number of pre-IND meeting requests default to written responses only (WRO), and in most cases when this occurs, there is often a need to follow up on the written comments with a request for a teleconference to clarify the comments. Therefore, as the pre-IND meeting

request is in many cases the first interaction between the Sponsor and the Agency, we strongly recommend that a pre-IND meeting request should be honored with a teleconference or face-to-face meeting. This is optimal to ensure mutual understanding of any outstanding items and path forward to IND submission.

- Initial IND Teleconference: BIO recommends establishing communication (teleconference) with Sponsors three to five days prior to the Day 30 communication to convey any final issues in instances where there are substantial concerns from FDA. Instituting a standard practice of scheduling a teleconference will ensure the Sponsor team and FDA have availability to discuss any critical issues, if needed, before the IND is in effect.

End of Phase 2:

- Establishment of a Mechanism for a Sponsor to Request a Debrief Meeting for End of Phase 2 (EOP2) Meetings: We recommend establishing a mechanism that allows a Sponsor to discuss with FDA revisions that the Sponsor has made to the development program following the EOP2 meeting prior to the start of Phase 3 trials. These meetings could be held four to six weeks after the EOP2 meeting completion and would ensure alignment on the feasibility of the registration objectives and design of registrational studies. Clear alignment between FDA and the Sponsor will contribute to more efficient development through the minimization of regulatory risks.

- Target Product Profile Feedback: We request that more divisions follow the Target Product Profile (TPP) guidance and provide specific feedback to Sponsors. It would be beneficial to Sponsors if FDA feedback is obtained earlier in development, such as at the EOP2 meeting or in conjunction with Phase 3 SPA review, so adjustments can be made by the Sponsor.

Documenting Meeting Outcomes:

- Rectifying Differing Interpretations of Meeting Outcomes: Review Divisions provide their minutes to the Sponsor and often indicate that the Sponsor should let them know if there are areas of disagreement; however, there is often no further follow-through or mechanism for updating the minutes or receive greater clarity. The best practices guidance should address this issue and outline a mechanism for the Sponsor and FDA to resolve these issues within 90 days, including alignment on actions that the Sponsor has taken to address the issue raised in the meeting minutes.

- Extending Meeting Times to Allow for Process Issues: Formal meetings in which live meeting minutes are taken by FDA and reviewed with the Sponsor should be extended to 90 minutes. Many Review Divisions now take live meeting minutes and review for agreement with the Sponsor during the meeting. While there are many advantages to the practice of reviewing minutes, it takes time away from discussion at the meeting, leaving insufficient time for some discussion topics. Extending the meeting time to 90 minutes and advising the Sponsor of the amount of time FDA is reserving for minute review allows time for the primary purpose of the meeting (discussion of Sponsor questions and FDA responses), as well as live review of minutes/agreement on discussion outcome.

C. Improving Communications between FDA and Sponsors Regarding Emerging and Evolving Science

For companies working on a cutting edge technology in an emerging scientific field, it is essential that they communicate with FDA frequently and effectively so that all parties fully understand the state of the underlying science and the regulatory pathway to approval. In some instances, FDA thinking may be actively evolving and guidance may not exist for emerging issues, which may lead Review Divisions to provide inconsistent recommendations to Sponsors. This in turn can make it difficult for Sponsors to apply learnings to subsequent development programs. FDA should seek to ensure that changes in their thinking regarding novel or emerging areas of science and medicine are communicated to Sponsors in an efficient manner.

- Inclusion of External Experts: For many evolving scientific fields, it may be beneficial to include leading external experts in FDA-Sponsor meetings in order to best evaluate the clinical development and review procedures. FDA should work with Sponsors in these cases to ensure that consultations with external experts occur at the appropriate times during the drug development and review processes in order to ensure an effective process based on the best available science.

- Staff Briefings with Sponsors: Some Review Divisions, such as the Division of Oncology Products, hold meetings where Sponsors are invited to discuss their development programs. These briefings provide a forum for scientific dialogue outside of specific program meetings. We recommend adopting this best practice across Review Divisions. We also suggest that other divisions more consistently hold Applicant Orientation Meetings (AOMs). These meetings allow Sponsors to provide a guided overview of the application to FDA staff and/or give summaries of key attributes in the submitted data to help the Agency make its risk-benefit assessment. All staff within a division are invited to attend these AOMs and ask any questions. These meetings provide FDA staff the opportunity to learn about many aspects an application and provide the Sponsor with some early insights into the types of questions that may be asked during NDA/Supplemental New Drug Application (sNDA) review.

- Responses Informed by Other Development Programs: It is valuable for a Sponsor to receive input from FDA for a development program based on knowledge and/or experience FDA has gained from other programs. While we understand that the Agency must adhere to limitations to ensure confidentiality, FDA should continue to provide generalized input from other development programs without disclosing confidential information. Where appropriate, FDA should acknowledge to the Sponsor that their generalized feedback is informed by experiences gained through other development programs.

- Responses Where Broadly-Applied Policy Questions Arise: We recognize that in many instances during drug development, new policy questions may arise that apply more broadly to other products in development. In many cases, these questions are time-sensitive and a venue needs to be available where these questions are addressed in a timely and efficient manner that is transparent. We recommend FDA leverage their established committee framework (*e.g.,* CDER Medical Policy Counsel,[4] Pharmacology/Toxicology Coordinating Committee,[5]

[4] CDER MAPP 4301.1, "Center for Drug Evaluation and Research Medical Policy Council"

Statistical Policy Coordinating Committee,[6] Regulatory Project Management Coordinating Committee,[7] and Carcinogenicity Assessment Committee[8]) to help answer policy questions during the drug development phase in a timely and efficient manner. Additionally, as these policy questions have broad application, those discussions and subsequent answers should be made public in a timely manner.

- Increased Inter-Office Communication toward Improving Consistency of Information to Sponsors: Communication and coordination within CDER and between CDER and other Centers (*e.g.,* CDRH) can be inconsistent, potentially causing program delays. For example, there have been times where a division within an office has provided guidance that differed from another division within the same office. For example, with respect to a Pediatric Study Plan (PSP), one office may indicate that the same PSP can be submitted to multiple INDs, while another office may ask for a PSP tailored to a single indication. Additionally, we continue to note a lack of cohesive process for programs that involve multiple FDA Centers, specifically CDER/Center for Biologics Evaluation and Research (CBER) and CDRH. We believe FDA's best practices guidance should address inter-Center communication and coordination regarding combination products and companion diagnostics to ensure that the appropriate Center/Division responds to questions directly related to their area of responsibility and expertise, and that there is formal coordination between Centers when developing Agency feedback or a position on topics overlapping between Centers/Division.

D. Improvements to Communication on FDA Website

- Establishment of FAQ Pages: The Agency may create a series of Sponsor-oriented frequently-asked-questions (FAQ) pages for topics for which the Agency receives common questions. This can reduce the call/email volume to PMs for routine information. The *FDA 101 for Industry* initiative represented a good first step for basic information, but answers to more intermediate or advanced common questions would be welcome.

- Availability of Existing FDA Policy or Guidance: Regulatory transparency and clear articulation of FDA's policies through guidance documents and other avenues can help to foster effective communication. Before contacting FDA, Sponsors should always check FDA's website for background information and guidance documents on the topic. However, this information is not always clearly available on the FDA website or the guidance may be outdated. We encourage FDA to continue to enhance its website, with a specific focus on ensuring that regulatory policies and requirements are readily accessible and identifiable. We recommend that FDA should consider developing a more systematic approach that ensures that guidance and other information that reflects the Agency's current thinking is easily accessible. In the case where information has become outdated, we recommend that FDA employ practices to communicate issues

[5] CDER MAPP 7400.1, "Management of the CDER Pharmacology/Toxicology Coordinating Committee and Its Associated Subcommittees and Working Groups"
[6] CDER MAPP 6610.1, "Statistical Policy Coordinating Committee"
[7] CDER MAPP 7500.1, "Regulatory Project Management Coordinating Committee"
[8] CDER MAPP 7412.2, "Management of CDER Carcinogenicity Assessment Committee and Communication of Committee Proceedings"

related to product development and review in a "current state of science" context, such as through Advisory Committees.

- FDA Website Search Engine: With the vast amount of information available on FDA's website, it is challenging for even experienced users to navigate the website. We request that the Agency enhance the search function within the FDA website. It is often easier to use Google to locate information on the FDA website than to navigate or search within the FDA website.

- Posting of Presentations Given by FDA Staff: We recommend that all presentations given by FDA should be posted on the FDA's website. This will allow for easier access and wider dissemination of information pertinent to Sponsors.

E. CONCLUSION

BIO appreciates this opportunity to comment on the "Best Practices for Communication Between the Food and Drug Administration and Investigational New Drug Sponsors During Drug Development." BIO believes that effective best practices for FDA-Sponsor communication implemented through FDA guidance and training will help to further advance biomedical science and improve patient access to novel therapies. As indicated above, in January 2015 we expect to complete an initial analysis of the second phase of a BIO member survey concerning FDA-Sponsor interactions in connection with nearly 200 clinical programs, and will provide that analysis to the FDA. In addition, we would be pleased to provide further input or clarification of our comments, if it would be helpful to the Agency.

Sincerely,

/S/

Andrew J. Emmett
Managing Director, Science and Regulatory Affairs
Biotechnology Industry Organization (BIO)

Appendix

FDA Effective Communications Survey

Prepared for: BIO

6 November 2013

Table of Contents

Objective & Methodology

OBJECTIVE

- To measure the effectiveness of the communications between FDA and sponsors during the drug development (Pre-IND through Product Approval) and determine ways to improve communication.

- This study focuses on overall communication between FDA and sponsors, not specific interactions in detail. Specific interactions will be investigated in the Continuous Journal study.

METHODOLOGY

- PSB conducted a 30-minute online survey **n=102** BIO members representing **91 companies** between June 18th and September 14th, 2013.

- This study represents the first wave of the annual survey. It will be repeated in 2014 and 2015.
    - A follow-on to this annual survey is the Continuous Journal, an online survey portal where members will be able to log their FDA interactions, while the experience is still fresh in their minds.
    - The questions posed in the Continuous Journal will be specific to individual interactions with the FDA and will assess each interaction separately.

A majority of companies surveyed have <250 employees and make <$25M in revenue

- 56% of companies surveyed have no products on the market
- Respondents mostly included those in regulatory affairs (53%) followed by CEO/Senior Management (42%)

Size of Company

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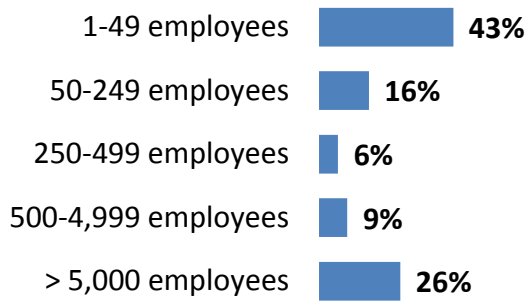
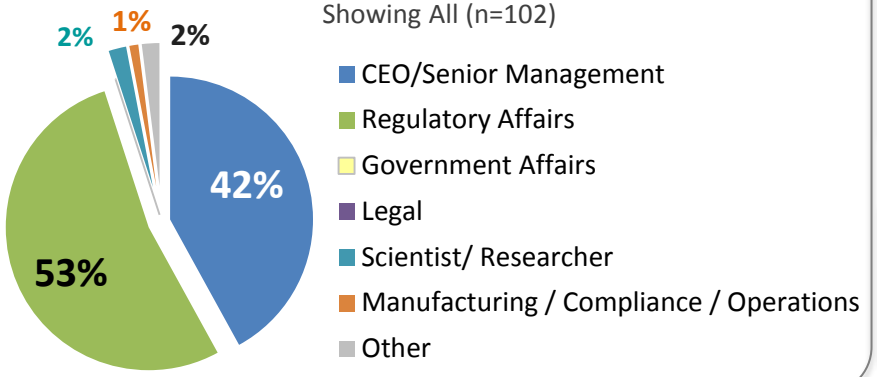


Job Function

Showing All (n=102)



of Products on the Market

Mean: **13.3**

Range: **0 - 200**

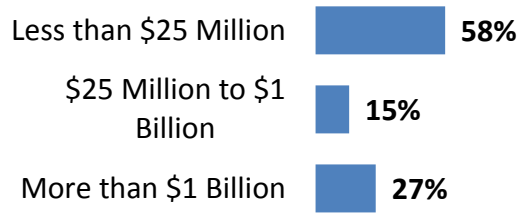
of Products in Development

Mean: **12.7**

Range: **0 -130**

Revenue Level

Showing All (n=102)



Phase of most advanced drug / clinical development program

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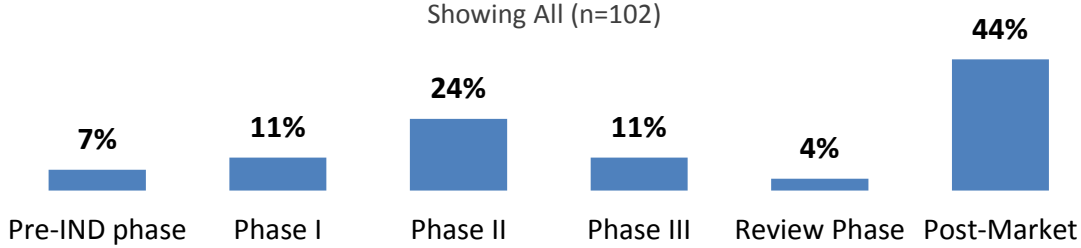


Key Findings

While satisfaction with communications between FDA and Sponsors is trending upward there are critical areas that could be improved

- The overall communication satisfaction rate is trending up from 64% in 2007-2010 to 70%
    - Members are most satisfied about communications regarding Priority Review and Breakthrough Therapies
    - Members are least satisfied about communications regarding BLA and Non-NME applications
    - Respondents reported wide variability in communication satisfaction across FDA review divisions
        - Members are most satisfied with CDER Oncology interactions
    - Satisfaction with quality of communication with the FDA appears to decline the later the product is in the FDA regulatory process
    - Respondents reported a higher satisfaction rate for in-person meetings (52%), and less satisfaction for the effectiveness of written letters and informal communications
        - Written letters and informal communications had similar levels of dissatisfaction (bottom 2 box 30% and 31% respectively)

Timely response from the FDA is critical to communications at all stages of development

- Timeliness of response is the leading complaint of companies that indicate FDA communication is poor/fair; Likewise, expeditious feedback is most frequently cited as a factor contributing to successful FDA communications
    - Timeliness of response saw the greatest improvement since 2007

Key Findings

Respondents reported both advantages and disadvantages of different avenues of communication depending on the particular context of the information request and timeliness of response

- Formal Meetings are most useful when Sponsors are seeking documentation / binding decisions
  - 34% had an FDA formal meeting request denied, namely because the FDA said informal communication was sufficient
- Informal meetings are useful under the right circumstances when documentation is not required
  - BIO members identified many examples of when informal FDA communications can be used (i.e., clarification / procedural questions)

Increase clarity of communications may be key to alleviating delays

- Members attribute miscommunication to a delay in product development for 40% of BIO members
  - The primary cause of delay was unexpected FDA reinterpretation of an existing agency policy

Need to raise awareness of the SPA procedure and the new Enhanced Communication Liaison Office

- 96% of BIO members have never contacted the new Enhanced Communication Liaison Office
- 74% of BIO members have never used the SPA procedure
  - 78% of those that did utilize a SPA had multiple reviews

Key Findings

Satisfaction ratings have improved since 2007

- Timeliness of responses major factor in improvement

Satisfaction ratings vary depending on type of application and stage of development

- Sponsors were the most satisfied with Priority Review applications (52%)
- Sponsors were the least satisfied with BLA (18%) and Non NME (19%) applications

Levels of dissatisfaction ratings increase with products in the review and post-approval stages

Miscommunication still a significant factor in product delays

- 40% of sponsors cited miscommunication with FDA as the main factor in one or more product delays

Key Findings

Satisfaction ratings vary depending on type of communication

- In-person formal meetings had the highest level of satisfaction (52%)
- Written letters (30%) and informal communications (31%) had similar levels of dissatisfaction

Satisfaction ratings vary significantly among review divisions

- CDER Oncology and CBER Cellular and Gene Therapies divisions had very high rates of satisfaction
- CDER Neurology, Pulmonary/Allergy/Rheumatology, Anesthesia/Analgesia/Addiction had very low rates of satisfaction

Vast majority of participants have not heard of the new Enhanced Communications Liaison Office

Only 25% of participants have utilized a SPA

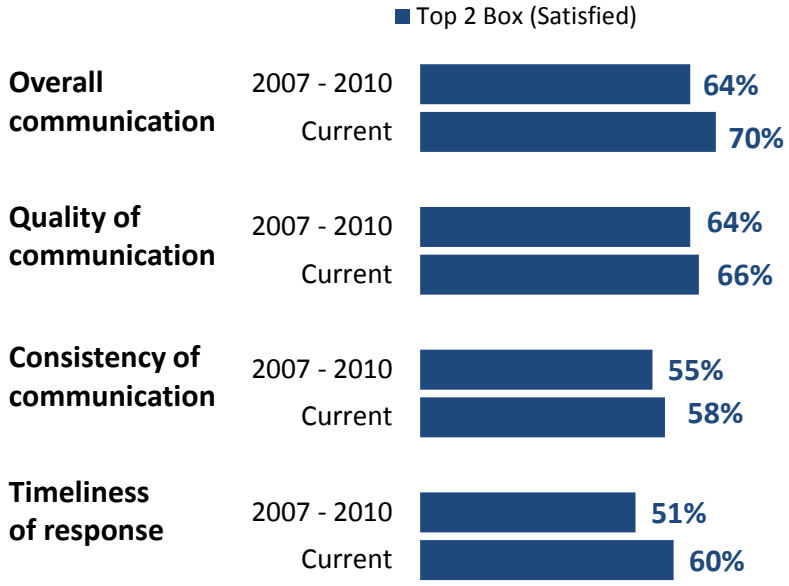
- 78% of SPAs utilized required multiple submissions

DETAILED FINDINGS

Overall, companies' levels of satisfaction with FDA interactions have improved slightly since 2007

- Companies are mostly/completely satisfied with overall communication
- Satisfaction with FDA communications has improved since 2007 (+6%)
- 'Timeliness of response' saw the greatest improvement in level of satisfaction since 2007. Currently 60% (+9%) are satisfied (top 2 box=Mostly/Completely Satisfied)

g14a+b. **Please rate your level of satisfaction with the following interactions your company had with the FDA during drug development between 2007 and 2010 / current (i.e., early in the implementation of PDUFA IV).**
Showing All (n=102)



	Product on Market		Most Advanced Phase			
	Yes (n=45)	No (n=57)	Pre or PhI (n=18)	Ph II (n=24)	Ph III / Review (n=15)	Post-Approval (n=45)
	A	B	C	D	E	F
Overall communication	64%	63%	50%	75%	60%	64%
	71%↑	68%↑	61%↑	75%	67%↑	71%↑
Quality of communication	62%	65%	67%	67%	60%	62%
	64%↑	67%↑	67%	71%↑	60%	64%↑
Consistency of communication	51%	58%	50%	62%	60%	51%
	51%	63%↑	67%↑	62%	60%	51%
Timeliness of response	40%	60% A	56%	71% F	47%	40%
	51%↑	67%↑	72%↑ F	67% F	60%↑	51%↑

Letter indicates the % is significantly higher than the other column indicated (at 95% confidence interval)

Additional comments provided about satisfaction mainly highlight individual challenges

While some point to issues with slow and challenging communication, many believe FDA communications have improved

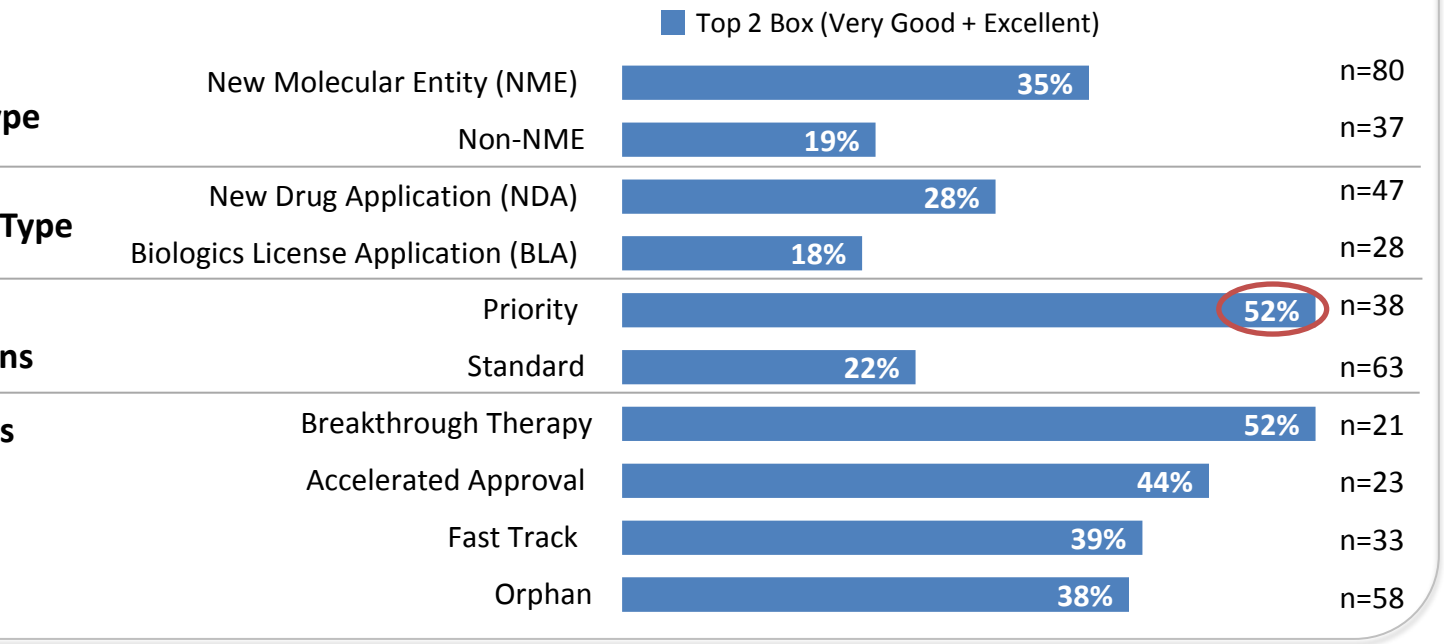
q18. **Please provide any additional comments you wish to share regarding the level of satisfaction with your company's communication with the FDA now vs. between 2007 and 2010 (i.e. early in implementation of PDUFA IV). Please be specific in your response.** OPEN END *All (n=102)*

- "Meetings denied then agency not coming back with written comments on topics; **Late comments** received prior to meetings, feedback at times the day before or of the meeting; Communication has been consistent but **not necessarily clear**."
- "For the time periods indicated, we have had a variety of both positive and negative experiences with FDA regarding its communication. For example, some review divisions like Oncology and CNS have provided good, timely communication. **Others, such as Pulmonary, have been more challenging**. Also, CDER leadership has provided great communication, while CDRH has been more problematic (although improving). Striving for more consistently good communication should be a goal for the FDA."
- "**The FDA Project Manager (PM) influences the level of satisfaction**. We have had competent PMs during this period who were engaged, responsive and intelligent. We also had a PM who was [not-responsive]."
- "Response has been **slow** and often confusing especially with terminology."
- "E-mail and informal communications are sometimes confusing and non-transparent. **Face-to-face meetings have worked best.** The most common challenge is when the FDA review team members have different opinions and-or level of risk tolerance and-or understanding of science-development plan."
- "**Turnover** of personnel led to some delays in answers and communication."
- "Incrementally it seems the **FDA is becoming more open & efficient** under PDUFA IV."
- "Generally, the group's experience has been that communication has **been better recently** than in the past."

BIO members are least satisfied about communications regarding BLA and Non-NME applications

- BIO members were most satisfied about communications with Priority applications (52%) and Breakthrough Therapy Designations (52%)
  - *Note*: n=28 of the n=102 BIO members surveyed have experience with both priority and standard review classifications
- BIO members were least satisfied about communications with BLA (18%) and Non-NME (19%) applications

g19. **Thinking of products your company has had in development since 2010, please rate the quality of FDA-Sponsor communication by application type and designation:** Rated on scale of: Poor, Fair, Good, Very Good, Excellent, and NA
Showing All with Experience in each category (Note: N/A responses were removed)

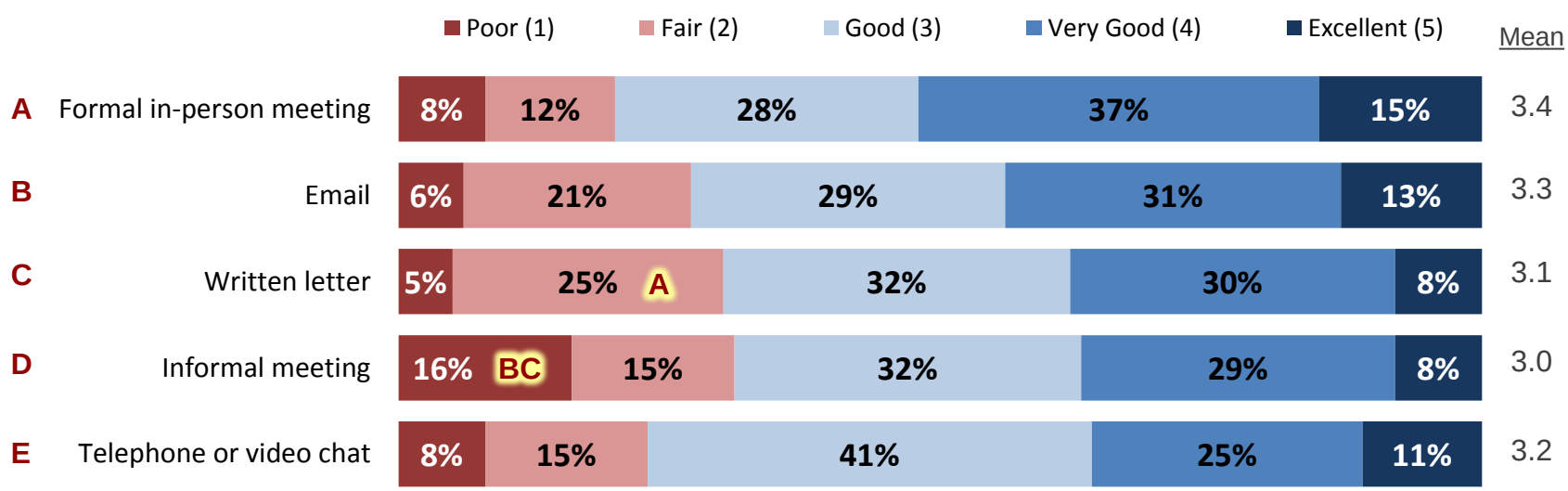


Significantly greater (at 95% confidence interval) than Standard Review Classification

Formal meetings are the most effective means of communication overall

- Respondents reported a higher satisfaction rate for in-person meetings (52%), and less satisfaction for the effectiveness of written letters and informal communications.
- Written letters (30%) and informal communications (31%) had similar levels of dissatisfaction (bottom 2)

g29. **Based on your current experience, please rate each of the following in terms of their effectiveness in communications with the FDA during drug development.** *Showing All (n=102)*



Letters indicate the % is significantly greater (at 95% confidence interval) than other row indicated by the letter code indicated on the left

Formal in-person meetings are the most effective means of communication overall

- Significantly more companies without a product on the market than companies with a product on the market rate **written letters** and **email** as being an effective means of communication (top 2 box)

- Satisfaction with communications is ranked the lowest in the post-approval stage for all types of communication except **informal meetings**

g29. **Based on your current experience, please rate each of the following in terms of their effectiveness in communications with the FDA during drug development.** *Showing All (n=102)*

Showing top 2 box (Very Good + Excellent)		Product on Market		Most Advanced Phase			
	ALL	Yes (n=45)	No (n=57)	Pre or PhI (n=18)	Ph II (n=24)	Ph III / Review (n=15)	Post-Approval (n=45)
		A	B	C	D	E	F
Formal in-person meeting	52%	44%	58%	61%	54%	60%	44%
Email	44%	31%	54% A	61% F	50%	53%	31%
Written letter	38%	24%	49% A	50%	54% F	40%	24%
Informal meeting	37%	38%	37%	39%	29%	47%	38%
Telephone or video chat	36%	27%	44%	56% F	38%	40%	27%

Letter indicates the % is significantly higher than the other column indicated (at 95% confidence interval)

Ability to ask questions in real time, in-person is why members seek informal feedback

- Ability to directly engage FDA subject matter experts is important to companies with no product on the market and companies with products in the early stages of development
- Ability to ask clarifying questions in real-time is important to companies with products in the post-approval stages

q128. **When deciding whether to seek informal feedback or request a formal meeting with the FDA, what factors are most influential in leading you to seek informal feedback?** *Select all that apply. Showing All (n=102)*

	ALL	Product on Market		Most Advanced Phase			
		Yes (n=45)	No (n=57)	Pre or PhI (n=18)	Ph II (n=24)	Ph III / Review (n=15)	Post-Approval (n=45)
		A	B	C	D	E	F
The ability to ask clarifying questions in real-time	72%	78%	67%	61%	71%	67%	78% D
Faster FDA response to simpler questions	68%	78%	60%	56%	50%	80%	78%
Directly engaging appropriate FDA subject-matter expert	64%	51%	74% A	83% F	71%	67%	51%
No background package to develop	28%	31%	26%	33%	21%	27%	31%
Other	13%	20%	7%	0%	8%	13%	20% C

Letter indicates the % is significantly higher than the other column indicated (at 95% confidence interval)

Others Include:

- "The Neurology Division does not appear to allow us to contact subject matter experts outside the direct review team--this differs from other Divisions with which some of us have experience."
- "I work with my Project Manager at FDA to discuss the most appropriate route prior to submission. Transparency and interaction on Sponsor's part have a huge influence on your FDA relationship."
- "Informal feedback is helpful to finalize internal strategy and allows to have preliminary discussions that influence final internal decisions. Informal feedback is key to understand how the agency thinks about issues, particularly in areas not well discussed in guidelines. It also helps to inform and sometimes educate the agency-review on specific topics. Informal feedback does not replace formal feedback."
- "Do not want anything formally captured."
- "Inconsistent ability to contact FDA experts directly - it varies among divisions"
- "Less complicated logistics and coordination"

A documented FDA response that can be considered binding is most influential in leading a member to seek a formal meeting

- Significantly more companies with 5000+ employees (63%) than companies with less than 5000 employees (23%) state *formal PDUFA meeting goals, timelines, and metrics* are influential in leading to request a formal meeting
- Significantly more companies with less than 50 employees (70%) than companies with 50 or more employees (50%) state *meeting with the entire cross-disciplinary review team at once* is influential in leading to request a formal meeting

q129. **When deciding whether to seek informal feedback or request a formal meeting with the FDA, what factors are most influential in leading you to request a formal meeting?**
Select all that apply. Showing All (n=102)

	ALL	Product on Market		Most Advanced Phase			
		Yes (n=45)	No (n=57)	Pre or PhI (n=18)	Ph II (n=24)	Ph III / Review (n=15)	Post-Approval (n=45)
		A	B	C	D	E	F
FDA's response has been documented and can be considered "binding"	70%	73%	67%	72%	67%	60%	73%
FDA review of Sponsor data in advance of the meeting	64%	64%	63%	56%	71%	60%	64%
Forum for addressing more complex scientific questions	61%	64%	58%	39%	71% C	60%	64%
Meeting with the entire cross-disciplinary review team at once	59%	53%	63%	67%	67%	53%	53%
FDA's response has been vetted internally at FDA at multiple levels of the division	57%	62%	53%	44%	62%	47%	62%
Formal PDUFA meeting goals timelines, and metrics	33%	42%	26%	11%	33%	33%	42% C
Other	5%	7%	4%	0%	4%	7%	7%

Letter indicates the % is significantly higher than the other column indicated (at 95% confidence interval)

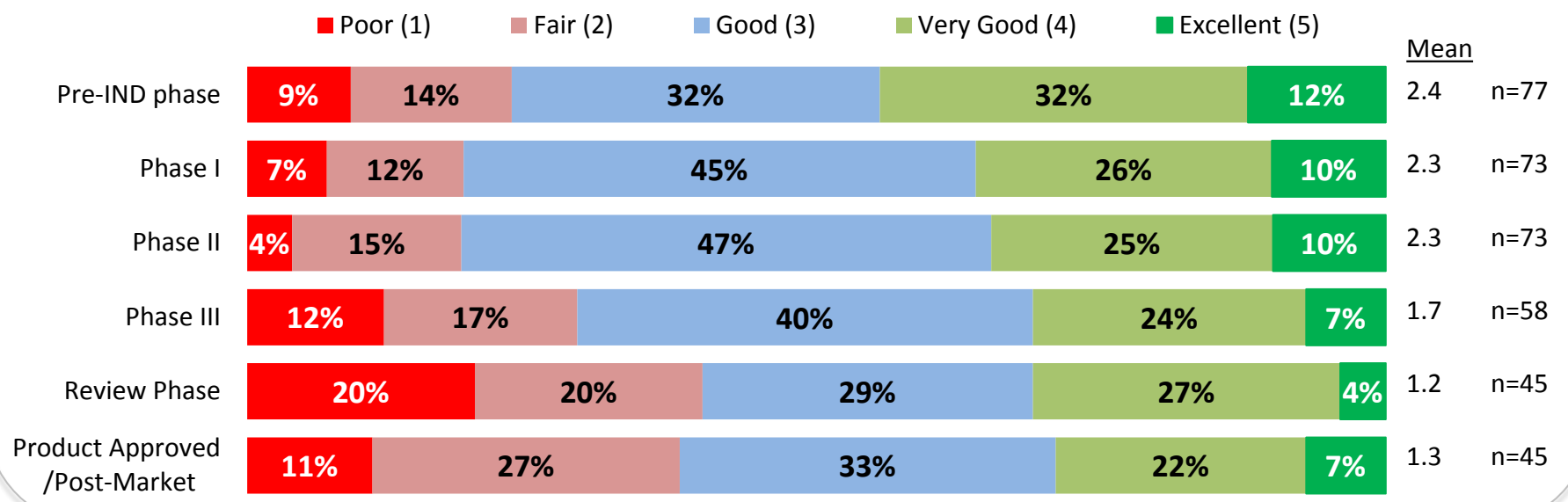
Others Include:

- "Having an opportunity to directly introduce the Division to the new technology and address any misconceptions at the earliest"
- "This is decided in consultation with the FDA Project Manager at DAVP."
- "It is the only option to get input"
- "Difficulty scheduling formal meetings"
- "Never sought feedback"

Quality of communication appears to decline in later stages of the FDA regulatory process

- BIO members are least satisfied with the quality of communications in the review phase
  - 1 in 5 BIO members rate communication in the review phase as poor

g84. **Please rate the quality of your communication with the FDA since 2010 by content type:**
(Showing All except those selecting NA)



Timeliness of response is the leading complaint of companies that indicate FDA communication is poor/fair

q90-95. **You indicated your company's communication with the FDA during the following stages of drug development since 2010 is either poor or fair. In your experience, what factors and unique considerations should FDA and Sponsors keep in mind to improve communication during the stages of drug development?** *OPEN ENDED*

[IF COMMUNICATION WITH FDA WAS POOR OR FAIR]	ALL (n=45)	Pre-IND (n=17)	Phase I (n=10)	Phase II (n=11)	Phase III (n=14)	Review Phase (n=17)	Product Approved (n=15)
Speed/Timeliness/slow response time	24%	-	10%	9%	14%	18%	40%
Meetings/accept requests for meetings	13%	29%	20%	-	-	-	-
Increased interaction/ communication/ more response	11%	6%	10%	-	-	24%	7%
Clarity/transparency	11%	-	-	-	7%	12%	13%
Mixed positives and negatives; adequate but could be better	9%	6%	10%	9%	-	12%	-
Advice/guidance is lacking	9%	12%	10%	9%	14%	-	-
Consistency/Conflicting information	9%	12%	-	9%	7%	6%	-
Not scientifically based	7%	-	10%	9%	-	-	7%
Advanced notice/communication	4%	6%	-	-	-	-	7%
Feedback on potential issues/concerns	4%	-	10%	-	-	6%	-
More informal interactions/communication	4%	-	-	9%	-	6%	-
Terms need to be better prepared for meetings	4%	-	-	9%	7%	-	-
RPM accessibility/responsiveness	4%	-	10%	9%	7%	6%	-
Communication with Project managers is lacking	4%	-	-	18%	-	-	-
FDA's lack on understanding	4%	12%	-	-	-	-	-
Be less condescending	4%	-	-	-	7%	-	7%
Nothing in particular	4%	-	-	-	7%	6%	-
Other	20%	18%	-	9%	21%	6%	13%
Don't know/no response	7%	-	10%	-	7%	-	7%

Likewise, timely feedback is most frequently cited as a factor contributing to successful FDA communications

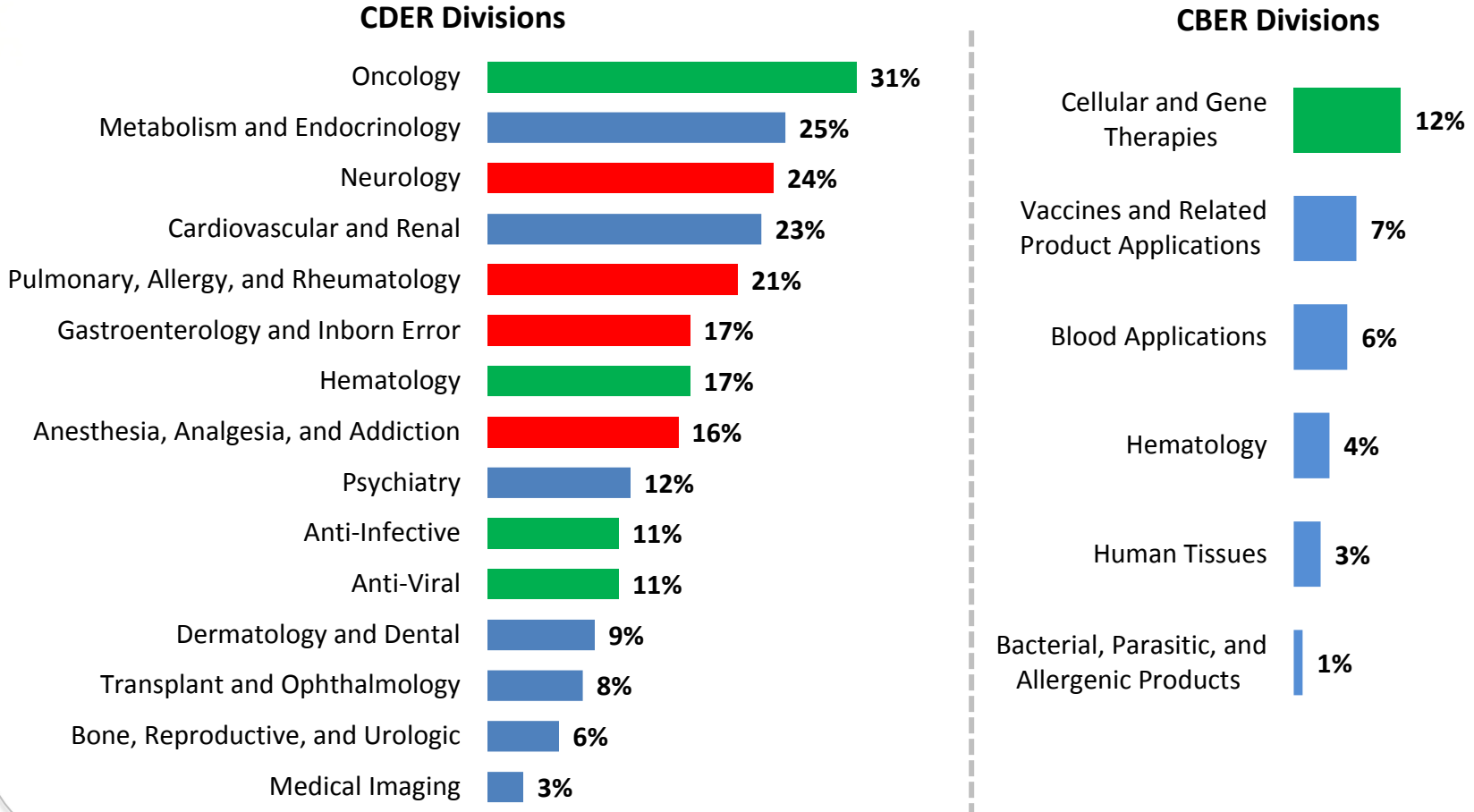
q96-101. **You indicated your company's communication with the FDA during the following stages of drug development since 2010 is either good, very good, or excellent. In your experience, what factors and unique considerations do you attribute to high quality communication with the FDA at each of the stages of drug development?** *OPEN ENDED*

[IF COMMUNICATION WITH FDA WAS GOOD, VERY GOOD OR EXCELLENT]

	ALL (n=87)	Pre-IND phase (n=55)	Phase I (n=48)	Phase II (n=50)	Phase III (n=32)	Review Phase (n=23)	Product Approved (n=21)
Timely Communication/Quick Feedback	24%	13%	21%	16%	9%	4%	10%
Clear/Transparent	16%	13%	6%	2%	9%	17%	19%
Helpful/Good Guidance/Advice	15%	11%	6%	8%	3%	4%	5%
Mixed positives and negatives	14%	2%	4%	10%	9%	17%	5%
Informative/Provides specific feedback	13%	7%	6%	8%	3%	-	-
Good communication with PM	11%	7%	6%	8%	12%	22%	10%
General positive: Good/Positive/No problems	11%	4%	4%	10%	-	9%	10%
Meetings/Responsive to meeting requests	10%	11%	6%	2%	3%	-	-
All negatives	8%	4%	2%	2%	6%	4%	5%
Responsive	8%	5%	-	8%	6%	-	5%
Accessibility of staff/project managers	6%	4%	2%	-	6%	4%	5%
Frequency of Communication	5%	4%	2%	-	3%	-	-
Nothing in particular	5%	-	4%	6%	6%	4%	-
Good feedback	5%	2%	4%	-	-	4%	-
Open dialogue/Interactive discussions	3%	-	4%	2%	-	-	-
RPMs do a good job	2%	-	4%	-	-	-	-
Other	16%	9%	12%	4%	9%	-	14%
Don't know/no response	14%	5%	4%	14%	12%	9%	14%

Oncology is the CDER Division most BIO members have interacted with since 2007

q34. **Please select all the review division(s) your company has interacted with during drug development since 2007.**
MULTIPLE RESPONSES PERMITTED (Showing All n=102)



Satisfaction with communications varies among Review Divisions

g35 + g57. **Please rate your level of satisfaction with the interactions your company had with the following FDA divisions during drug development.** *Rated on a scale of Completely dissatisfied, Mostly dissatisfied, Neither satisfied nor dissatisfied, Mostly satisfied and Completely satisfied i.e.Top2)*

	n=	Between 2007 and 2010 (i.e., early in the implementation of PDUFA IV) Top 2 Box	Since 2010 Top 2 Box	% Change
CDER Division of Oncology Products	31	81%	87%	+ 6%
CDER Division of Metabolism and Endocrinology Products	25	64%	56%	- 8%
CDER Division of Neurology Products	24	42%	54%	+ 12%
CDER Division of Cardiovascular and Renal Products	23	61%	70%	+ 9%
CDER Division of Pulmonary, Allergy, and Rheumatology Products	21	48%	48%	--
CDER Division of Gastroenterology and Inborn Error Products	17	41%	47%	+ 6%
CDER Division of Hematology Products	17	82%	75%	-7%
CDER Division of Anesthesia, Analgesia, and Addiction Products	16	44%	44%	--
CDER Division of Psychiatry Products	12	58%	58%	--
CDER Division of Anti-Infective Products	11	64%	73%	+ 9%
CDER Division of Anti-Viral Products	11	73%	73%	--
CDER Division of Dermatology and Dental Products	9	22%	33%	+ 11%
CDER Division of Transplant and Ophthalmology Products	8	62%	75%	+ 13%
CDER Division of Bone, Reproductive, and Urologic Products	6	67%	67%	--
CDER Division of Medical Imaging Products	3	67%	0%	- 67%
CBER Division of Cellular and Gene Therapies	12	75%	75%	--
CBER Division of Vaccines and Related Product Applications	7	57%	57%	--
CBER Division of Blood Applications	6	67%	67%	--
CBER Division of Hematology	4	75%	75%	--
CBER Division of Human Tissues	3	33%	33%	--
CBER Division of Bacterial, Parasitic, and Allergenic Products	1	0%	0%	--
CBER Division of Viral Products	0	--	--	

The top & bottom overall are highlighted in each column for divisions with n-sizes greater than 10. Respondents only rated divisions they have interacted with.

Communication with Project Managers (vs. Medical Reviewers) **and formal meetings** (vs. informal) **have the highest quality**

g79. ***Please rate the quality of your different types of communication with each division since 2010.***
(Showing N-size Reporting Top 2 Box)
Rated on a scale of Poor, Fair, Good, Very good, Excellent, and NA

	n=	Communication with Project Managers		Communication with Medical Reviewers		Formal Meeting Communication		Informal Communication	
		Top 2 Box	n=	Top 2 Box	n=	Top 2 Box	n=	Top 2 Box	n=
CDER Division of Oncology Products	31	70%	30	65%	26	77%	30	52%	27
CDER Division of Metabolism and Endocrinology Products	25	42%	24	32%	19	37%	19	27%	22
CDER Division of Neurology Products	24	39%	23	14%	21	52%	21	14%	22
CDER Division of Cardiovascular and Renal Products	23	71%	17	29%	17	38%	16	31%	16
CDER Division of Pulmonary, Allergy, and Rheumatology Products	21	47%	19	29%	17	39%	18	29%	17
CDER Division of Gastroenterology and Inborn Error Products	17	25%	16	15%	13	25%	16	13%	15
CDER Division of Hematology Products	17	67%	15	60%	15	87%	15	60%	15
CDER Division of Anesthesia, Analgesia, and Addiction Products	16	20%	15	29%	14	25%	12	14%	14
CDER Division of Psychiatry Products	12	58%	12	36%	11	60%	10	50%	10
CDER Division of Anti-Infective Products	11	27%	11	20%	10	43%	7	30%	10
CDER Division of Anti-Viral Products	11	64%	11	27%	11	30%	10	27%	11
CDER Division of Dermatology and Dental Products	9	0%	8	0%	8	25%	8	13%	8
CDER Division of Transplant and Ophthalmology Products	8	50%	8	40%	5	57%	7	43%	7
CDER Division of Bone, Reproductive, and Urologic Products	6	75%	4	60%	5	80%	5	80%	5
CDER Division of Medical Imaging Products	3	0%	3	0%	1	0%	1	0%	3
CBER Division of Cellular and Gene Therapies	12	55%	11	80%	10	80%	10	64%	11
CBER Division of Vaccines and Related Product Applications	7	43%	7	50%	6	50%	6	43%	7
CBER Division of Blood Applications	6	50%	6	33%	6	33%	6	33%	6
CBER Division of Hematology	4	75%	4	100%	1	50%	2	75%	4
CBER Division of Human Tissues	3	100%	2	100%	1	100%	1	67%	3
CBER Division of Bacterial, Parasitic, and Allergenic Products	1	0%	1	--	0	--	0	0%	1
CBER Division of Viral Products	0	--	0	--	0	--	0	--	0

The top & bottom overall are highlighted in each column for divisions with n-sizes greater than 10. Respondents only rated divisions they have interacted with.

Satisfaction varies by FDA division

q83. **Please provide any additional comments you wish to share on the quality of communication you have had with particular FDA divisions. Be as specific as possible in your response, noting the specific FDA division(s).** OPEN END

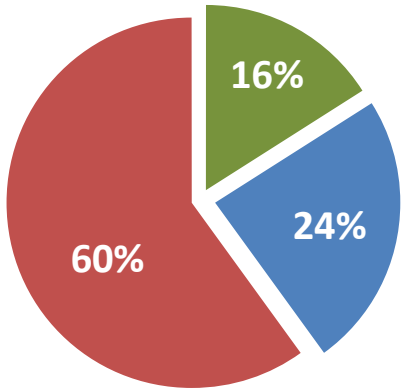
Showing All (n=102)

- "**Neurology Division** has frequently missed statutory deadlines, even for a Fast Track product in which we had to wait [several] months from the time of request for a meeting date and they then canceled the meeting the day before, informing us that they would instead send us a written response."
- "FDA review staff from the **Division of Oncology 1** seem very engaged with us as the sponsor; they read the Briefing Document prior to meetings and are prepared to discuss issues. Regarding the **Division of Antivirals**, it seems like the review staff had its mind made up before reviewing the Information presented."
- "It is difficult to rate communications to a particular Division because **not all RPMs function the same way**. I may have a great relationship with an RPM but may have difficult with another RPM within the same Division. **Consistency among Center-Office-Division is important.** Consistency among all RPMs is equally important."
- **"DPP** is timely and complete. **DAAAP** is always late and less than forthcoming. **DGI** is timely and complete."
- "**DAARDP** is much less transparent and trusting than **cardio-renal.** Their communications are less frequent and very formal. Cardio-renal team members are much more open and willing to work with you to find the best development plan-path forward. [Division Leadership] definitely can see the sponsor perspective and think about what can work for both parties involved."
- "The **Metabolism and Endocrine Division** has been very responsive. While the **Division of Hematology** could not meet the PDUFA timeline for a meeting, they did provide comments on the meeting questions 2 weeks in advance of the meeting."
- "During SPA process **Rheumatology Division** communications were unclear. **Cardio Division** - RPM was very responsive. "
- "The **Division of Hematology and Division of Oncology** have been more collaborative and open to discussion."

40% of respondents cited FDA-Sponsor miscommunication as a contributor to one or more delays in product development

- On average, these delays are quite long
  - 4 BIO members reported delays lasting 2 years
- Significantly fewer companies with a product on the market (42%) than companies without a product on the market (74%) had an FDA-Sponsor miscommunication contribute to a delay in product development

q102. **Did FDA-Sponsor miscommunication contribute to a delay in product development for any of your products currently in development?** Please only consider projects you've had in development since 2010. For example, did the perceived basis for approval shift during the development program or were significant new issues/concerns raised late in development? – *Showing All (n=102)*



- Yes, more than one product was delayed since 2010
- Yes, only one product was delayed since 2010
- No

q103a. [IF MORE THAN ONE PRODUCT EXPERIENCED A DELAY] **How many months was the most significant delay**? (Showing Mean)

14.3 months

q103. [IF ONE PRODUCT EXPERIENCED A DELAY] **How many months was the delay**? (Showing Mean)

9.4 months

Many delays experienced since 2010 stem from a lack of clarity in communication from the FDA

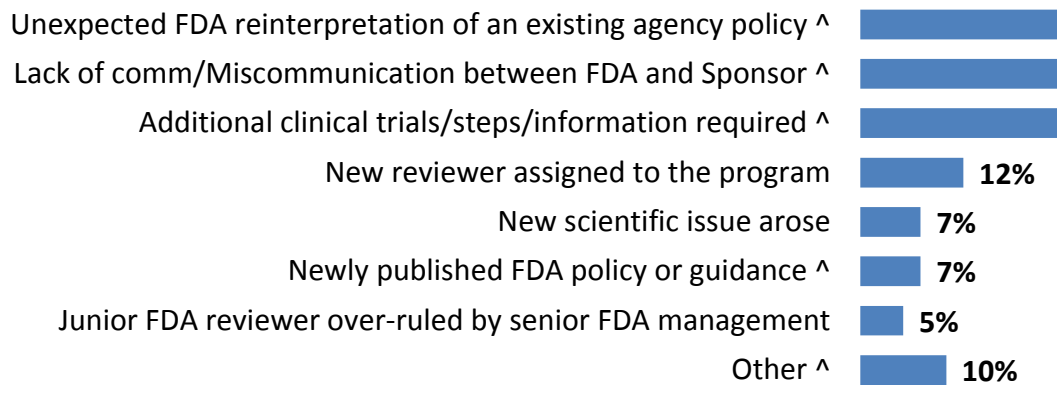
q104. [IF EXPERIENCED DELAY] **Please describe the most significant delay you experienced since 2010.**
OPEN END Showing All (n=41)

- **"Changed their mind** and required additional toxicity data right before NDA submission resulting in additional 8 months delay."
- **"Lack of clarity** on NDA content (3 pre-NDA meeting requests denied) resulted in an RTF."
- "Was not miscommunication but a lack of communication during the application review period. Despite previous positive feedback the division did not support approval. Through the review there was a **lack of clear communication** leading up to the decision. Early communications or transparency from the review division may have helped the sponsor and promoted open discussion of issues-concerns."
- **"Delay in approval** due to FDA not communicating issues with review early enough to address them during PDUFA first cycle."
- "Delays with a tox reviewer continually **asking for more information** and new experiments when evaluating carcinogenicity reports."
- **"Delay in review timeline** due to lack of effective informal communications of filing review issue before formal action taken."
- "Our delay occurred due to a change in use of statistical methodology as part of an adaptive trial design. We were placed on clinical hold even after we received initial FDA approval to use a different statistical method. While the issue was ultimately resolved, we were **delayed almost 3 months**. It appeared that FDA's stats group was in agreement with us, but the medical reviewers either did not initially understand our approach or were not aware of FDA's stats' support of our method."
- **"Delayed feedback** on appropriate trial design to progress development program to approval."
- "At our Type C meeting we were told the surrogate endpoint was acceptable to support approval. A year later, [FDA's position changed and] **data would be required confirming the surrogate is indicative of clinical benefit prior to approval even though the surrogate was previously used for full approval** for a product in the same population."

The primary cause of delay was unexpected FDA reinterpretation of an existing agency policy

- Miscommunication was the primary cause of delay in nearly 1 in 3 cases

q105. [IF EXPERIENCED A DELAY] **What was the primary cause(s) of the delay? Select all that apply.** *Showing All (n=41)*

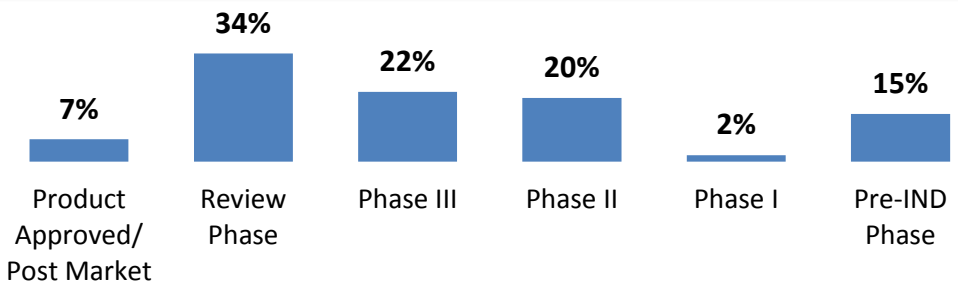


Other Responses Provided Include:

- "REMS"
- "Unsure- may have been the complexity of the proposed study or understaffing"

^ means that the category has been modified or newly created to include a portion of the 51% who originally indicated 'other'

q106. **At what phase of development did the delay take place?** *Showing All (n=41)*



Members seek clear and consistent communication from the FDA to avoid delays

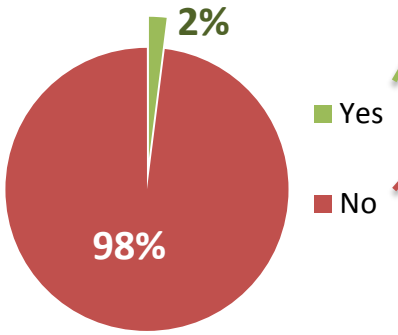
q107. [IF PRODUCT EXPERIENCED DELAY] **How could the delay have been avoided?** OPEN END Showing All (n=41)

- "FDA [should] be VERY **clear** as to their requirements and be internally aligned on decisions."
- "Had FDA **responded more quickly** (rather than in 6 months) to our initial proposal, we could have discussed their concerns and avoided the back and forth via written correspondence that ultimately delayed the submission."
- **"More effective communication** from RPM to sponsor including more than just communication of the issue. Proposed path to resolve issue was agreed to, but formal action taken prior to agreed date of resolution."
- "If FDA was **consistent in their guidance**."
- **"Clear expectations** from the FDA prior to not accepting clinical hold release package as complete."
- "Once PMC studies are completed the Division **should issue formal correspondence** that the PMC was complete. These should not necessarily be linked to the WR studies even if there was overlap in some of the requirements. Now we have an approved WR but not a PMC that has been fulfilled."
- "**Earlier communication** from FDA regarding issue and how it could be addressed before PDUFA date."
- "**More communication** between FDA and Sponsor."
- "Provide **consistent advice** agreed upon across the management levels. Ensure senior management understand the complete background before making a decision."
- "Allowing opportunity for **informal communication to clarify** simple issues rather than being subject to written responses and 30-60 day clock response timelines."
- **"Better, clearer communication** during development."
- **"Asking better questions** earlier."
- "Working together to solve a complex regulatory strategy for a devastating orphan disease in children. There is a need for **pragmatism** and **flexibility**, including innovative approaches."

Majority believe FDA communication/action did not accelerate product development

- BIO members report FDA communication was late or absent in many instances

q108. **Did FDA action or communication accelerate product development?** *Showing All (n=41)*



q109.[IF YES] **How did FDA accelerate product development?** *Showing All (n=1)*

"**Worked with us** to facilitate IND after that IRB delay"

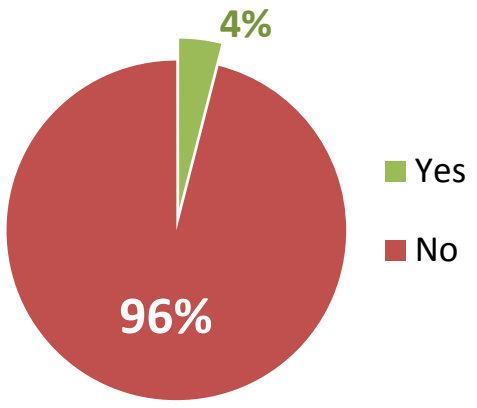
q110. [IF NO] **Why was FDA action or communication unable to accelerate product development?** *Showing All (n=40)*

- "Because the response was **late**."
- "FDA feedback was **unclear and not timely**."
- "There was **absence of communication** requests denied."
- "**Could never get FDA to comment** on product development."
- "FDA **did not communicate**."
- "**Required additional detail** that delayed the initiation of a trial"
- "This is **still an open issue**. FDA has expressed an openness to work with us to accelerate product development, and we are optimistic in that regard."
- "**Unwilling to support the original agreement** of standard approval."

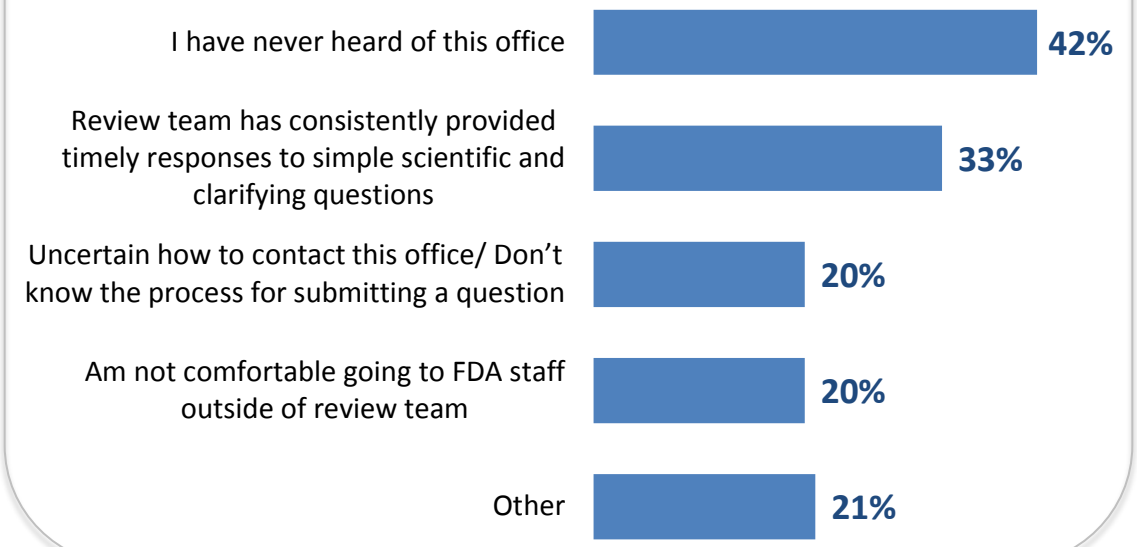
96% of BIO members have never contacted the new Enhanced Communication Liaison Office

There is great opportunity to increase awareness about this office as 42% say they have never heard of it and 1 in 5 are uncertain how to contact the office / don't know the process for submitting a question

q119. **Have you ever contacted the new Enhanced Communication Liaison Office to help answer a question?**
Showing All (n=102)



q120. [IF NO] **Why have you not contacted the Enhanced Communication Liaison Office? Select all that apply.**
Showing All (n=98)



Half of those contacting the Enhanced Communication Liaison Office had a procedural question

- Most questions were answered directly by the liaison staff in a prompt manner
- Telephone and Email were the main methods of communication

q121. [IF YES] **What was the nature of the most recent question you had for the Enhanced Communication Liaison Office? *Select all that apply.*** *Showing All (n=4)*

Jurisdictional question (i.e., Which FDA office handles…?)	n=2
Procedural question (i.e., How do I go about submitting…?)	n=2
Scientific question (i.e., During a toxicology study, do I need to conduct…?)	n=1
Other	n=2

- *"Call to EC office was to discuss lack of communication and delay in request for type A meting"*
- *"FDA representation on WHO Committee"*

q122. [IF YES] **How did you communicate with the liaison office about your most recent question? Select all that apply.** *Showing All (n=4)*

Telephone	n=3
Email	n=2
In-person meeting	-
Written letter	-
Video chat	-
Other	-

q124. [IF YES] **Regarding your most recent question, what was the outcome from the Liaison office?** *Showing All (n=4)*

My question was answered directly by the liaison staff	n=3
My question was directed to the review division staff	n=1
I was referred to a formal meeting	-
I received an estimated timeframe for an FDA response	-
I have not received any response to the question yet	-
Other	-

q123. [IF YES] **How long did you wait to receive a response about your most recent question from the review division before contacting the Liaison office?** *Showing All (n=4)*

My question was answered directly by the liaison staff	n=3
My question was directed to the review division staff	n=1
I was referred to a formal meeting	-
I received an estimated timeframe for an FDA response	-
I have not received any response to the question yet	-
Other	-

Liaison Office communication is prompt and BIO members are mostly satisfied with their ability to answer questions

q125. [IF YES] **How long did it take to receive a response to your question after contacting the Liaison Office?**
Showing All (n=3)

One day	n=2
One week	n=1
One month	
Longer than a month	

q126. [IF YES] **How satisfied were you with the Liaison Office's ability to answer your most recent question?**
Showing All (n=4)

Completely satisfied	-
Mostly satisfied	n=3
Neither satisfied nor dissatisfied	n=1
Mostly dissatisfied	-
Completely dissatisfied	-

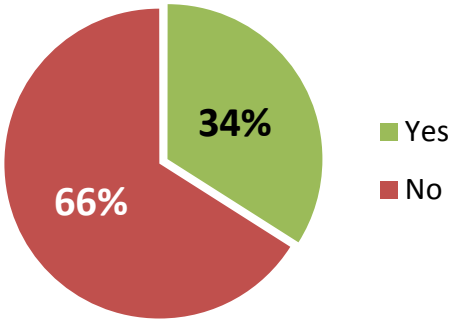
q127. **Please provide any additional comments you wish to share on your experience and best practices for engaging with the Liaison Office.** OPEN END
Showing All (n=4)

- "It is hard to rate the liaison based on my n=1 experience"
- "[The liaison office staffer] was very helpful"
- "It was a relatively straightforward question, for which an adequate response was received."
- "N-A"

34% have had an FDA formal meeting request denied, namely because informal communication was sufficient

< 50 employees = **20%**
50+ employees = **36%**

q130. **Have you ever requested a formal meeting with the FDA and had it denied?** *Showing All (n=102)*



q131.[IF YES] **What reasons were cited for not granting the meeting? Please select all that apply.** *Showing All (n=35)*

Informal communication was sufficient to resolve the issue / answer the question	31%
Meeting deemed unnecessary ✳	29%
Necessary parties could not be convened in for a formal meeting	14%
FDA wanted to respond formally in writing ✳	14%
Timing required faster turnaround than a formal meeting could offer	9%
Requirements not met/ New policies in place not met ✳	9%
FDA's response directed the formal meeting to be held with a different department	6%
Not enough resources/information ✳	6%
Meeting request was submitted incorrectly	3%
No Reason ✳	3%

Note: 60% of total respondents answered "other".
Their answers were grouped into the categories marked with a ✳

Members would like more clear, consistent and timely feedback from the FDA during a SPA

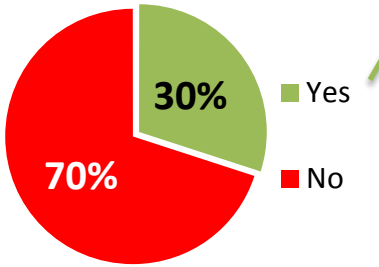
q118. **What are best practices for FDA-Sponsor communication during a Special Protocol Assessment? Be as specific as possible in your response.** OPEN ENDED *Showing All (n=27)*

- "Attempt to **resolve 'minor' issues** within SPA process rather than requiring second SPA submission (where possible)."
- "Call a **milestone meeting** immediately after the non-agreement letter is issued."
- **"Provide all expectations** of a complete SPA package upfront. If charters are required need to know upfront. Need harmonization in expectations and requirements across divisions."
- "Need to provide **clarity** on what is and is not expected regarding the SPA process/submission. The agency did not advise on a way to correct issues resulting in the SPA being withdrawn; Repeated SPA cycles due to outstanding operational topics."
- "FDA [was] open to explor[ing] and accept[ing] alternative approaches/measures to make the trial execution more feasible while solving the concerns. Sponsors need to be detailed and specific in questions to FDA, submit SPA and [meet] full expectations of what FDA will require, be scientific; expect review will go beyond 45 days. FDA has provided very detailed thoughtful responses, appreciate the additional suggestions and comments. If 45 day clock cannot be met advise sponsor sooner then later to effectively plan study activities."
- "Need to **provide clarity** on what is and is not expected regarding the SPA process-submission. The agency did not advise on a way to correct issues resulting in the SPA being withdrawn; Repeated SPA cycles due to outstanding operational topics."
- "If a SPA review is delayed, it would be useful for FDA to **communicate to the Sponsor** the reasons for the delay and to keep them apprised of any progress."
- "Clear, concise comments so that the sponsor knows exactly what needs to be revised to obtain an agreed upon SPA."
- **"Timely communication** enabling sponsor to provide updated documentation during the process rather than require a second submission."
- "Give **feedback on modifications** that would be required before the 45 day close deadline to allow Sponsor to modify and preserve 45 day deadline for agreement."
- "Per guidance, **we always request a Type B meeting prior to SPA submission and get FDA feedback on the majority of the questions for the SPA.** For our latest one, we were able to negotiate small changes via e-mail during the 45 day review time. For other SPAs, we have needed to request a Type A meeting to get additional feedback. In one case, the timeline for this Type A was 60 days so be patient."

30% of BIO members have experienced a clinical hold from the FDA since 2010

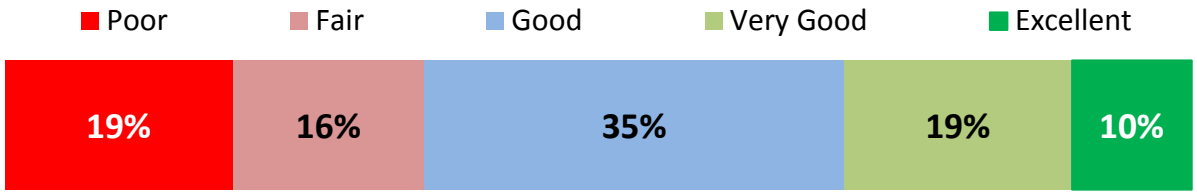
- Respondents that have experienced a clinical hold…. Satisfaction with communications with FDA is a mixed bag
- Significantly more CEOs (70%) than Regulatory Affairs representatives (19%) rate the FDA communication as ineffective (Bottom 2 box: Poor + Fair) leading up to and during the clinical hold(s).

q111. **Have you experienced a clinical hold from the FDA since 2010?** *Showing All (n=102)*



[IF YES] According to FDA policy, if a clinical hold is imposed, the specific reasons for the clinical hold should be clearly specified in the clinical hold letter to the Sponsor of the IND. Further, FDA is expected to attempt to discuss and satisfactorily resolve the matter with the Sponsor before issuing the clinical hold order.

q112**. How would you rate the effectiveness of FDA communication leading up to and during the clinical hold(s)?** *Showing All (n=31)*



During a clinical hold, clarity and earlier communication /review are areas that BIO members believe can be improved

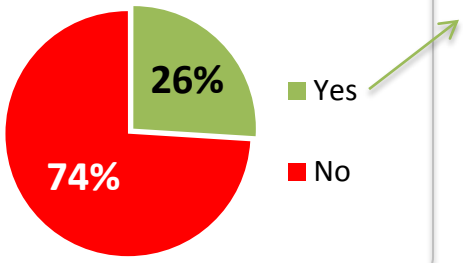
q113. **What current FDA communication practices need to be improved during a clinical hold?** OPEN END
Showing All (n=31)

- "**Clarity** for the scientific rationale behind the decision."
- "**Clear expectations** from FDA."
- "The **specific reasons** for the hold need to be more clearly delineated in the clinical hold letter."
- "When FDA places IND on partial hold, we need something in writing that documents we can proceed. We need **documentation of a change** to the clinical hold circumstance."
- "Better attempts to resolve both before and after the hold. **Internal oversight and review of holds**."
- "There was nothing in the communication by the FDA leading up to the clinical hold letter that was any different than what was conveyed in the clinical hold letter (ie no attempt to discuss/satisfactorily resolve the matter before the letter). There should be a **greater attempt to make the pre-letter communication more effective** in order to allow the sponsor sufficient time and or ability to resolve issues. In addition, writing a continued clinical hold letter should not be used as a mechanism to 'buy time' for the agency to complete review of documents or to request or raise additional issues. There should be adequate communication during the clinical hold process - for both the sponsor and the agency to clarify requests."
- "**Earlier communication** of potential clinical hold decision to allow sponsor to actively correct before clinical hold is decided; **Timely response** to sponsor's clinical hold response submissions."
- "During the IND review (30 days) - **issues could be raised earlier** to enable sponsor to respond and avoid the clinical hold."
- "Allowing for **informal communication** to clarify simple issues, rather than being subject to written response and 30-60 day response cycle periods."
- "Ideally, the Division would **review information submitted in partial response** to clinical hold but it is possible that no review is done until the sponsor declares a complete response."
- "CMC reviewer did not ask the questions well and Project Manager did not pull together teleconference until after 30 day review period. Issue was resolved by Company once teleconference was held with led CMC reviewer. **Led CMC reviewer needs to get involved earlier.** Project manager needs to hold teleconference if first round of questions generates more questions."

1 in 4 BIO members have used the SPA procedure
(There may be a need to increase awareness about SPA)

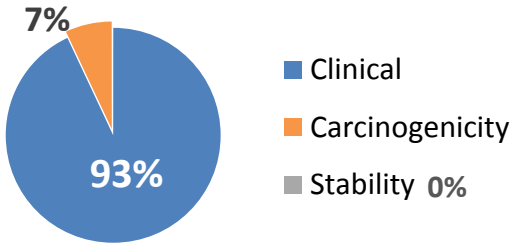
- Significantly more companies with 50 or more employees (36%) than companies with less than 50 employees (14%) have used the SPA procedure since 2010
- 78% of SPAs utilized required multiple review cycles with FDA

q114. **Have you utilized the Special Protocol Assessment (SPA) procedure since 2010?** *Showing All (n=102)*

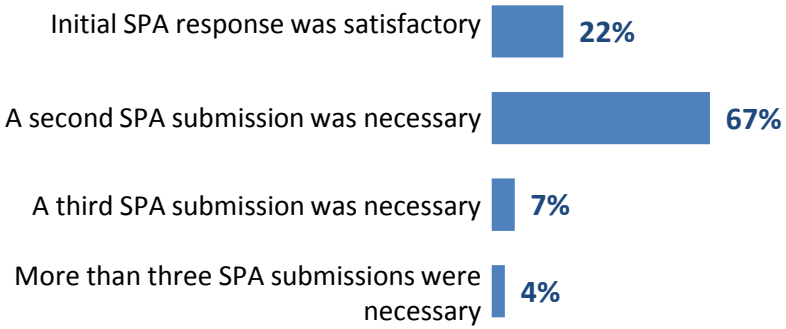


Significantly more have 5000+ employees (44%) than less than 50 employees (14%)

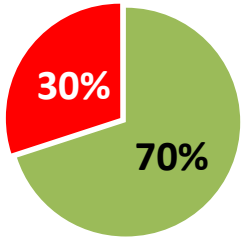
q115. [IF YES] **In your most recent SPA submission, what SPA procedure did you use?** Note: If you had more than one SPA response, please answer in terms of your most recent experience. *Showing All (n=27)*



q116. [IF YES] **Was the initial SPA response satisfactory or was it necessary to undergo multiple SPA submissions to resolve issues and enable the study to commence?** *Showing All (n=27)*



q117. [IF YES] **Were you able to reach an agreement and have a finalized SPA prior to the start of your trial? If yes, please specify the number of days it took to finalize the SPA.** *Showing All (n=27)*



Average of ~90 days to finalize the SPA

BIO members identify a variety of issues that the FDA should be able to address with informal communications including approach/procedure changes and clarification questions

q132. **BIO members have identified the following as simple scientific issues. Can you think of any other examples of a simple scientific issue that FDA should be able to address utilizing informal communications (i.e. email or phone call)?**

- A minor additional toxicity finding in an IND-supportive toxicity study
- A dosage change in a Phase 1 clinical trial
- Adjustment of an adverse event parameter in a Phase 1 clinical trial
- Minor variability in impurity profile in an early manufacturing

OPEN END *Showing All (n=102)*

CHANGES TO THE APPROACH / PROCEDURE

- "Overall approach for comparability during Phase 1-2. Capture of non-related adverse events in protocol. Minor changes in manufacturing process."
- "Modifying inclusion criteria for good clinical reasons."
- "Reasons for hold up of review."
- "Amount of stability data needed to extend shelf life."
- "Design of a tox study"
- "Minor modification of inclusion-exclusion criteria in any clinical trial."
- "Minor protocol amendment"
- "Platform changes for endpoint measurements."
- "Non-scientific questions on procedure should be easier to address informally."

CLARIFICATION

- "Clarification of expectations for drug interaction study."
- "Clarification on submission types, i.e., CBE0 vs CBE30 vs PAS."
- "Clarification of a procedural issue. estimated timing-review-feedback on a major amendment."
- "Clarification of rationale for selecting a particular statistical test."
- "Procedure questions such as 1 day delay of a briefing document"
- "Improper classification of drug-device combination product."
- "Question on analytical testing requirements for release vs. stability testing."
- "Proposal for presentation of information and requesting FDA's agreement."

Next Steps – Continuous Online Journal

- n=68 respondents said they would be willing to be invited to participate in the continuous online journal
- Invite individuals in the sponsor company, who lead their NDA/BLA submissions, to provide feedback about the nature of their communications with the FDA
- Individuals will be encouraged to journal about member company experience about an individual single drug development program
- PSB and BIO will co-create the design of the journal and the questions to be asked about each FDA interaction
    - New respondents will be required to answer a few questions up front and then will be able to continue to the journal to provide their insight
    - Returning respondents can be taken directly to the journal where they can create an entry about a new FDA interaction

THANK YOU

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Melissa Blunck
Vice President of Research, Healthcare

Hilary Modjeska
Director, Healthcare