

HOW HAS THE FDA'S AND THE MEDICAL PRODUCTS INDUSTRY'S USE OF
GUIDANCE DOCUMENTS EVOLVED OVER THE YEARS AND HOW WILL THE USE
OF GUIDANCE DOCUMENTS CONTINUE TO EVOLVE IN THE FUTURE?

by

CHRISTOPHER MATTHEW BROWN

(Under the Direction of Gary Dykstra)

ABSTRACT

Due to the extremely wide range of medical products being governed by the same few sets of general regulations, the FDA has created a system of documents to guide and direct manufacturers on how to apply those regulations to specific types of products. How those documents are used and how effective they are at providing adequate guidance was determined through a series of phone interviews with FDA and medical products industry personnel.

In general, the guidance document system works well for both the industry and the FDA. However, some improvement is desired in the process for creating and revising guidance documents due to the long, multiple-stage process currently in place.

INDEX WORDS: FDA, Guidance, Guidance document, Medical products industry,
Regulations, Good guidance practices, GGP

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DEDICATION

This body of work is dedicated to my loving family. My wife, Jennifer, and my children, Julia and Joshua, were my motivation and my biggest supporters in completing this thesis and other degree requirements.

I also dedicate this body of work to my grandfather, William F. Barnes, who was my greatest role model and my inspiration in trying to better myself through higher education.

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CHAPTER 1

INTRODUCTION

FDA Introduction

The Food and Drug Administration (FDA), currently an agency in the United States Department of Health and Human Services, was created in 1848 when Caleb Beck of the Patent Office received an appointment “to carry out chemical analyses of agricultural products, a function that the newly created Department of Agriculture (USDA) inherited in 1862”¹. Later this task was given to Dr. Harvey Wiley, Chief Chemist of the USDA’s Bureau of Chemistry. Under the direction of Dr. Wiley, great strides were made to protect consumers from adulterated foods and drugs, including the passing of the 1906 Pure Food and Drugs Act, which paved the way for modern FDA functions¹. The present name of the organization was created in July 1930, and the FDA became a part of what is now known as the Department of Health and Human Services in 1940².

The modern FDA has responsibility for “protecting the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products, medical devices, [the] nation’s food supply, cosmetics, dietary supplements, and products that give off radiation, . . . advancing the public health by helping to speed product innovations . . . [and] helping the public get the accurate, science-based information they need to use medicines and foods to improve their health”³. The FDA accomplishes its mission by

enforcing the Food, Drug and Cosmetic Act (FD&C Act) that replaced the Pure Food and Drugs Act in 1938. The FD&C Act and its many amendments, plus assorted other federal laws⁴, provide the framework for the authority and responsibility of the FDA. From these acts and amendments, the FDA develops regulations by a process known as the rulemaking process, which is laid out in the Administrative Procedures Act (APA) of 1946 and which the agency adopted in the form of regulations in 1975⁵.

Laws, Regulations and Guidance Documents

Laws like the FD&C Act are created and passed by the United States Congress through a complex bill-making process. A bill passed by Congress is then sent to the President, who may either sign the bill into law or veto it. Once a bill is signed into law, it becomes a part of the United States Code (USC), and an enforcement agency, such as the FDA, is charged with ensuring compliance with the law. In the case of the FDA, this law is then broken down into regulations. As regulations are created by the FDA, they are added to Title 21 of the United States Code of Federal Regulations (CFR), which contains the FDA's regulations. These regulations are, in general, very broad in scope due to the wide range of products which they are intended to regulate. For example, Part 820 of Title 21 (21 CFR 820) is intended to be used in regulating the quality systems of all medical device manufacturers, regardless of whether it's a complex implantable product, such as a pacemaker, or a simple disposable product such as a surgical glove⁶.

In the 1967 case of *Abbott Laboratories v. Gardner*, the U.S. Supreme Court held that the regulations issued by the FDA in the Code of Federal Regulations had the "force and effect of

law”. Since that time, the process of creating new regulations has become more and more complex, time-consuming and costly⁷.

In addition to regulations, the FDA has created a system of guidance documents to provide additional insight into how the FDA interprets these broad regulations. These guidance documents are intended to be used by the agency staff and members of the regulated industry so that all interested parties have the same understanding of the FDA’s expectations. Unlike regulations, guidance documents are not equivalent to laws, and therefore, are not legally binding for either the FDA or to those members of the industries that the FDA regulates^{8,9}.

Guidance documents are created and revised through a comment-and-revision process. In this process, the FDA posts the document on the internet and puts a notice of where the document may be viewed in the Federal Register, “the official daily publication for rules, proposed rules, and notices of Federal agencies and organizations, as well as executive orders and other presidential documents”¹⁰. Once posted, the public is given an opportunity to provide comments to the FDA on the draft version. After a specified length of time, the comments are collected and reviewed by the FDA to determine which, if any, should be implemented into the final version of the document. Once the reviews and document revisions are complete, the document is published as a final version and a notice posted in the Federal Register with an assigned effective date¹¹.

Reforming the Rulemaking Process

Since 1975, when the FDA adopted the rulemaking process as outlined in the Administrative Procedures Act of 1946, efforts have been made by Congress to reform the FDA’s rulemaking process⁵. Although several attempts at reform legislation were made, it was

the 104th Congress of the United States that finally passed four crucial pieces of rulemaking reform legislation in the name of small business relief “from burdensome regulations”⁵. The first piece of legislation was the Unfunded Mandates Reform Act of 1995, which set limits to the allowable size of expected expenditures of non-government resources to achieve compliance without federal funding to cover costs¹². Its intent was to protect small businesses from being burdened by large expenses required to achieve and maintain compliance with government regulations⁵.

The remaining three pieces of rulemaking reform legislation were bundled together and passed by Congress in 1996 as a bill also aimed at relieving small businesses from excessive burdens caused by laws and regulations⁵. These acts, the Small Business Regulatory Enforcement Act, the Congressional Review Act and amendments to the Regulatory Flexibility Act of 1980, all had significant effects on the rulemaking process⁵. With these reformation acts, FDA rules, including regulations, are subject to Congressional review before being put into effect. The result is that new rules may not become effective for several months and may never become effective at all if vetoed by Congress. In addition, the FDA is required to provide several types of impact studies and analyses to Congress as part of the review, including foundational studies, cost analyses, and other information and analysis pertaining to the regulation and its effect on the industry and consumers of the industry’s products⁵. With these and other reforms in place, there are likely to be fewer changes made to regulations. Furthermore, any changes made are likely to be broader in scope in order to encompass the wide range of products being regulated. This is due to the vastly increased costs and utilization of FDA resources required to submit new rules or rule changes to Congress. Therefore, the use of guidance documents has become even more important in allowing the FDA to communicate to the public and the

regulated industry its interpretations of the laws and regulations and how the FDA expects industry to comply with those laws and regulations⁵.

CHAPTER 2

GUIDANCE DOCUMENTS

History of Guidance Documents

Guidance documents have existed in one form or another since the passing of the 1938 FD&C Act when the FDA began to periodically release a document called the *Trade Correspondence* that contained excerpts and commentary on correspondence with members of industry. The intent of the *Trade Correspondence* was to help maintain uniformity in how FDA policy was enforced. However, the *Trade Correspondence* was not published. It was only available for public inspection at FDA headquarters or in field offices around the country¹³. The first true guidance for industry was not available until 1949 when the FDA published the document entitled: *Procedures for the Appraisal of the Toxicity of Chemicals in Foods* in which the FDA explained to food manufacturers how to test for the safety of food in animals¹⁴.

Good Guidance Practices

The Food and Drug Administration Modernization Act (FDAMA) of 1997 had a significant impact on the guidance document creation process. FDAMA “codified portions of the agency’s good guidance practices (GGPs)” by “adding statutory provisions for guidances” to the FD&C Act¹⁵. The FDA responded by issuing its final rule for developing and issuing guidance documents in September 2000¹⁵.

By definition, the good guidance practices (GGPs) are “FDA’s policies and procedures for developing, issuing, and using guidances”¹⁶. This set of regulations, found in 21 CFR 10.115, defines what types of documents are to be considered guidance documents and, for the sake of clarification, provides examples of documents that are not to be considered guidance documents, such as FDA internal procedures, press materials, and warning letters¹⁶. Guidance documents are classified into two levels. Level 1 guidance documents are those that cover more complex or controversial issues or set new policies or significantly alter current policies. All other guidance documents are considered Level 2 and generally include documents that are less controversial and complex.

Level 1 guidance documents have a strict set of regulations for implementation including posting a notice in the Federal Register, posting the document on the internet, and soliciting public comments. The FDA may also hold public hearings or send the document for review by an advisory committee, a formal committee generally made up of members of the regulated industry, advocacy groups, and other recognized experts in the field. The FDA then revises the document based upon feedback and comments received about the draft version from the various sources. The revised document is published as a final version, and a notice is posted in the Federal Register to inform the public of the new final document and the implementation date.

Level 2 guidance documents are much simpler to implement. They are made available on the internet, and a notice is posted in the Federal Register. In the case of Level 2 documents, they may be implemented immediately and then revised again if deemed necessary after receiving public comments or other feedback.

Over the years, guidance documents have become more and more important as a communication tool between the FDA and regulated industry. One reason for this is the commonly held perception that the rulemaking process, by which formal regulations are created, is “both time-consuming and resource-intensive”¹⁵, especially when compared to the less formal process by which guidance documents are created. The value of guidance documents is their ability to communicate “the agency’s current thinking on a particular subject” to both the FDA personnel and the medical products industry members in one document rather than requiring the FDA to respond “individually to questions and inquiries from stakeholders”¹⁵.

Evidence of this increased importance of guidance documents may be found by comparing the number of new rules and regulations with the number of new guidance documents for a period of time. Seiguer and Smith determined that between January 2001 and November 2003, there were approximately twice as many guidance documents issued as rules and regulations¹⁵. This is a clear indication that the rulemaking process slows the creation of new rules and regulations when compared to the how the GGPs affect the creation of guidance documents.

Guidance documents are not without their drawbacks. As previously discussed, the implementation of Good Guidance Practices, as required by FDAMA, drastically slowed the FDA’s ability to create new guidance documents, especially for new medical technologies, where guidance documents are critical in communicating FDA’s views on compliance. Several officials with the FDA have voiced concerns “about the increased layers of review for guidances” and that “additional scrutiny of guidances may detract from their utility as they become less flexible and responsive”¹⁵. Regardless of the criticism of the GGPs, those same officials agreed that guidance documents were the “best means of providing information to assist

industry in understanding and complying with regulatory requirements”, especially considering the “rapid pace of scientific advancement” in the medical products field¹⁵.

United States v. Utah Medical Products, Inc.

Although guidance documents are not legally binding to either the FDA or to the FDA-regulated industries, FDA personnel are instructed to comply with guidance documents unless there is “appropriate justification” for noncompliance and the employee receives “supervisory concurrence”⁹. Therefore, one might be concerned that FDA inspectors or new product reviewers could, at times, fail to separate their own requirements, as discussed in guidance documents, with the requirements of the inspected company, as specified in the regulations. In other words, since the broadly-worded regulations have only established *what* manufacturers are required to do, inspectors and reviewers may become overly dependent on guidance documents, which frequently discuss *how* manufacturers must perform these tasks⁶.

In the case of the *United States v. Utah Medical Products, Inc.* of 2005, the FDA attempted to seek an injunction against Utah Medical Products for failure to meet the validation regulations in 21 CFR 820. Utah Medical Products contested the FDA’s claims arguing that just because the methodology used in the validation of their processes did not match industry standards or the methodologies discussed in various guidance documents, did not mean that the validations, as performed, did not meet the requirements in the Code of Federal Regulations. The court agreed when it held that the FDA’s claims were not valid and that Utah Medical Products was in full compliance⁶.

This landmark case appears to be the result of FDA personnel confusing compliance to the regulations with compliance to the guidance documents. Although the FDA claims that no

policy changes were implemented as a result of this ruling⁶, it certainly served as a reminder to the FDA and the regulated industry that regulations are legally binding but guidance documents are not.

Study Methodology

To answer the question: *How has the FDA's and the Medical Products Industry's use of Guidance Documents evolved over the years and how will the use of Guidance Documents continue to evolve in the future?*, one must look beyond the history books and periodicals. The real answers may be obtained from the regulators and the regulated. By extracting opinions and other such information from these industry experts through personal interviews, one can gain insight into the FDA's and industry's perceptions of guidance documents.

By conducting a series of phone interviews with members of the medical products industry and current and former employees of the FDA, sufficient data was collected to analyze and form conclusions about past and future guidance document usage. These interviewees included persons representing the pharmaceutical, biologics, medical device, and veterinary products manufacturers; the FDA; and the regulatory consultant industry. The purpose of the interviews was to collect opinions, thoughts and ideas with respect to guidance documents and their usage and effectiveness. In addition, interviewees were queried to ascertain whether any alternatives to the current guidance document process might be appropriate.

Since this project involved conducting personal interviews of experts to obtain their thoughts and opinions on a subject, this was considered to be human subject research. As such, it was subject to review by an institutional review board (IRB). The University of Georgia IRB reviewed and approved the proposed project and assigned it project number 2010-10642-0.

The criteria for selecting persons to interview was established based on the type of data desired. FDA personnel were selected based on their areas of expertise. Those who specialized in medical products or guidance document creation and who agreed to the informed consent statement were allowed to participate. A mixture of personnel working at FDA headquarters and FDA field offices was obtained. Industry personnel were also selected based on their areas of expertise. Candidates holding regulatory affairs positions in medical products companies or regulatory affairs consulting companies and who agreed to the informed consent statement were allowed to participate. Due to limitations in time, language, and budget, all candidates chosen were located in the United States. Target participation was set at 25 participants per respondent pool. Although this target was not met in either pool, the responses collected were so consistent from respondent to respondent for many questions that conclusions could still be drawn on the population as a whole even with the smaller than desired sample size.

The questions chosen for these interviews were designed to capture a broad array of facts and opinions on the demographics of the respondents, guidance document usage and effectiveness, the guidance document system itself, and any potential changes or improvements desired by the respondents. Care was taken to ensure these questions would, when answered, provide adequate data to develop conclusions that would answer the thesis question. Where possible, questions intended for the FDA respondents and the industry respondents were the same or very similar to facilitate comparisons between the responses of the two groups. However, due to the different perspectives of these two groups, this was not always possible. To streamline the analysis process, minimize interviewer bias and provide more meaningful results, likely answers to interview questions were predetermined in a multiple choice format. After the questions and potential likely answers had been formulated for both groups, they were validated

by conducting three interviews of each type and verifying that the questions and possible answers were appropriate. Only minor phrasing issues were identified and corrected.

At the conclusion of these interviews, analysis of the resulting data was conducted to look for similar opinions or patterns of thought between the respondents. Analysis consisted of developing histograms of the data to determine if there were any correlations between the subject groups and their opinions. The objective of these analyses was to provide supporting data to the answer of the thesis question. Comparisons were made between the data collected and pre-research hypotheses about how guidance documents are used and viewed by industry and the FDA. Conclusions were drawn about the perceived effectiveness of the FDA Guidance Document system and about improvements that could be made to it.

Hypotheses

Based on research conducted before beginning the interview process, it was hypothesized that if FDA respondents and industry respondents were synchronized in their thoughts and opinions on guidance documents, they would agree with each other in terms of the perceived effectiveness of guidance documents and in their support of guidance documents as a regulatory tool in general. However, it was thought that some in industry might have expressed interest in making some changes to current and future guidance documents in the interest of harmonization with the Global Harmonization Task Force (GHTF), International Organization of Standardization (ISO) and International Conference on Harmonization (ICH) standards and guidance documents.

It was hypothesized that if FDA personnel are required to follow guidance documents except in special circumstances and then only with supervisor consent¹¹ and industry personnel

are eager to prevent compliance issues with the FDA, then both groups would feel like management is fully supportive of guidance document usage. Alternatively, it was also conceivable that industry personnel would be split on the issue of management support of guidance document usage. For example, it was hypothesized that if small companies and companies with a small medical products division had limited regulatory expertise, then they might not have sufficient management awareness of guidance documents to be considered supportive or may rely on consultants more for regulatory advice rather than guidance documents. Similarly, companies with combined quality and regulatory management might have insufficient regulatory expertise resulting in a lack of awareness of guidance documents. Alternatively, larger medical products companies were likely to have strong regulatory expertise at high levels resulting in policies being developed based directly on guidance documents.

It was hypothesized that if the creation of the Good Guidance Practices slowed the process of creating and revising guidance documents and guidance documents are an integral part of maintaining compliance with regulations, then both industry and FDA personnel would feel as though guidance documents required too much time and effort to create and revise and that efforts to streamline this process need to be initiated. Also, industry personnel were likely to be concerned about getting their products cleared or approved and into the market as expeditiously as possible. Since new product submissions are often created by following guidance documents, industry personnel were also likely to be concerned with how long it takes to finalize and publish guidance documents. This hypothesis was based on the assumption that industry respondents were likely to understand that new product submissions to the FDA, such as Pre-Marketing Approvals (PMAs) and 510k's for medical devices and New Drug Applications (NDAs) for pharmaceuticals, might be subject to review delays if the FDA decides more

information is needed, even if there is no guidance document in place to describe what specific information is required with the new product submission.

It was hypothesized that if both FDA and industry respondents treated guidance documents as not legally binding and guidance documents are useful in helping to understand the FDA's current thinking on regulatory matters, then both groups would be likely to state that FDA inspections and product reviews were reasonable in terms of not citing nonconformance with guidance documents, though some were likely to express concern about the current influx of new inspectors and the retirement of many well-experienced inspectors, a condition that is currently present in the FDA and which could result in new occurrences of past lessons, such as discussed in the case of the *United States v. Utah Medical Products, Inc.*

Overall, it was thought that both the FDA and industry respondents would be supportive of guidance documents and the Good Guidance Practices currently in place though some suggestions for improvement were likely to be made, especially with regards to the length of time required to create and publish a new document compared to the rate at which medical technologies are developing. Some respondents were even expected to offer the suggestion of scrapping the current guidance document system in lieu of a web-based system which explains specific requirements based on product parameters input by the user. However, in general, both parties were thought likely to be satisfied with the status quo and possibly be reluctant to incite change.

CHAPTER 3

MEDICAL PRODUCTS INDUSTRY RESPONSES

Demographics of Industry Respondents

During the course of this research, eighteen members of the Medical Products Industry agreed to participate in providing their insights and opinions on FDA Guidance Documents. The average number of years for the respondents working in the medical products industry was 23.6 years with a total range of 5 to 40 years. Of those eighteen respondents, eight had worked in more than one segment of the industry. Figure 1 depicts how many of the respondents had worked in each product segment during their career. Sixteen industry respondents had worked in medical devices; eight had worked in pharmaceuticals; three had worked in biologics; and one had worked in veterinary products.

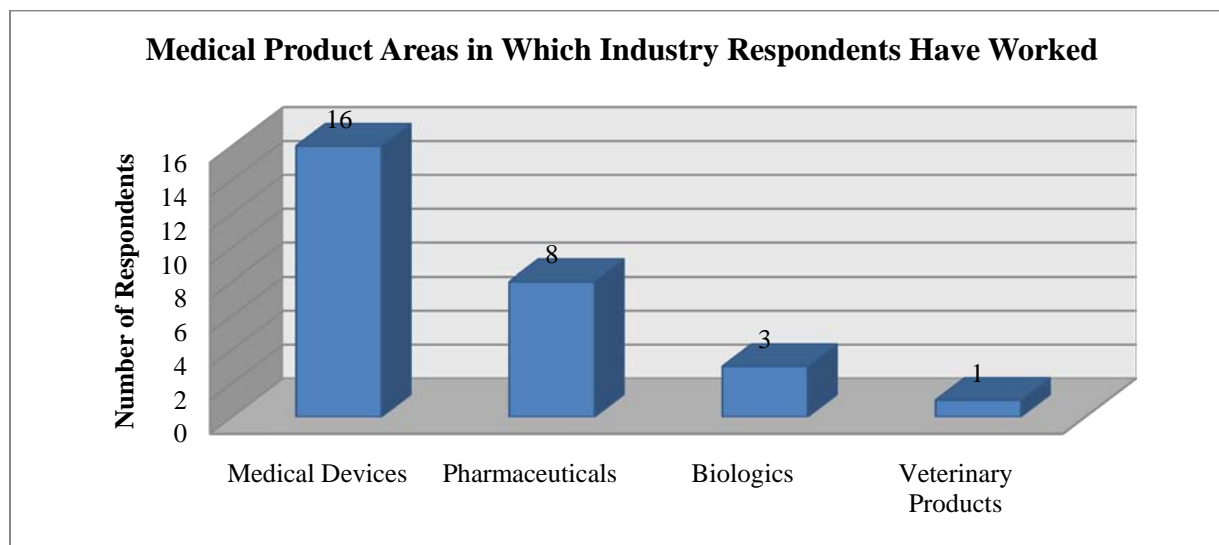


Figure 1 – Medical Product Areas in Which Industry Respondents Had Worked

Seven of the eighteen respondents were consultants in the Medical Products industry, but all had extensive experience in the industry prior to becoming consultants. These seven consultants all worked for companies of less than 50 people in size. Also, seven of the non-consultant respondents were employed by large companies of greater than 5000 people. The remaining three respondents were employed by smaller companies of 500 people or less. Figure 2 displays the breakdown of company size for the respondents.

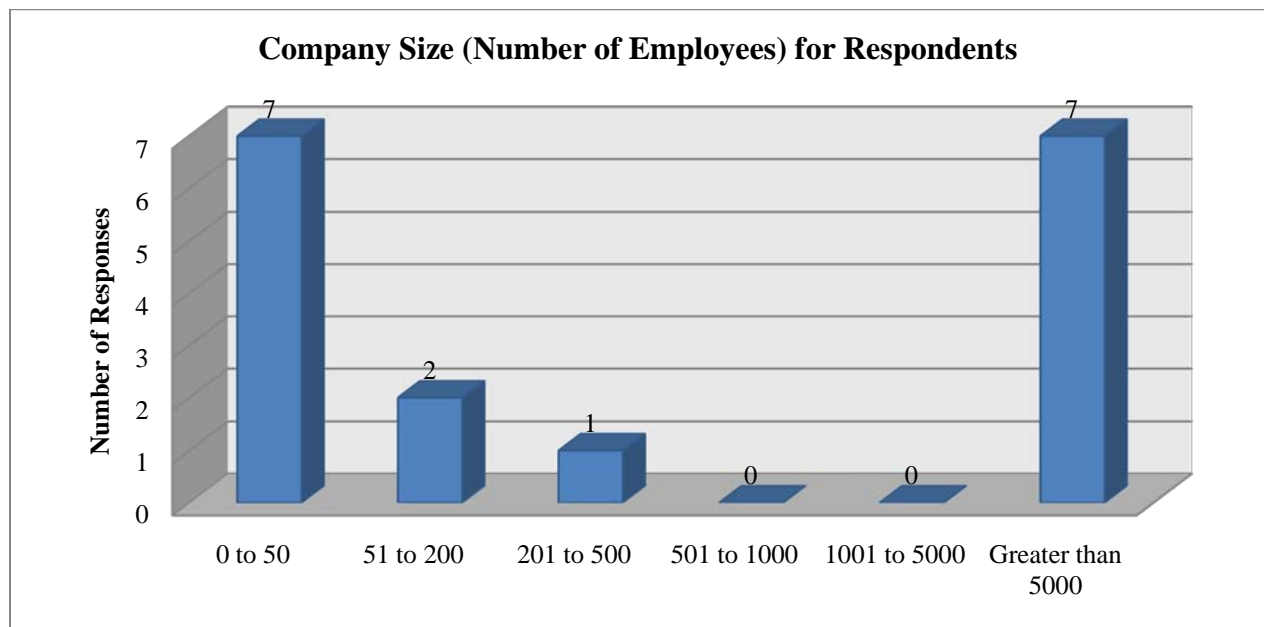


Figure 2 – Company Size (Number of Employees) for Industry Respondents

Of note was that the majority of industry respondents were considered to be in upper management level positions (i.e. director, vice president or president). Contributing to this skewed statistic was the fact that all seven of the consultant respondents were also considered upper management in their consulting firms. Figure 3 depicts the levels of responsibility within their firm held by the respondents.

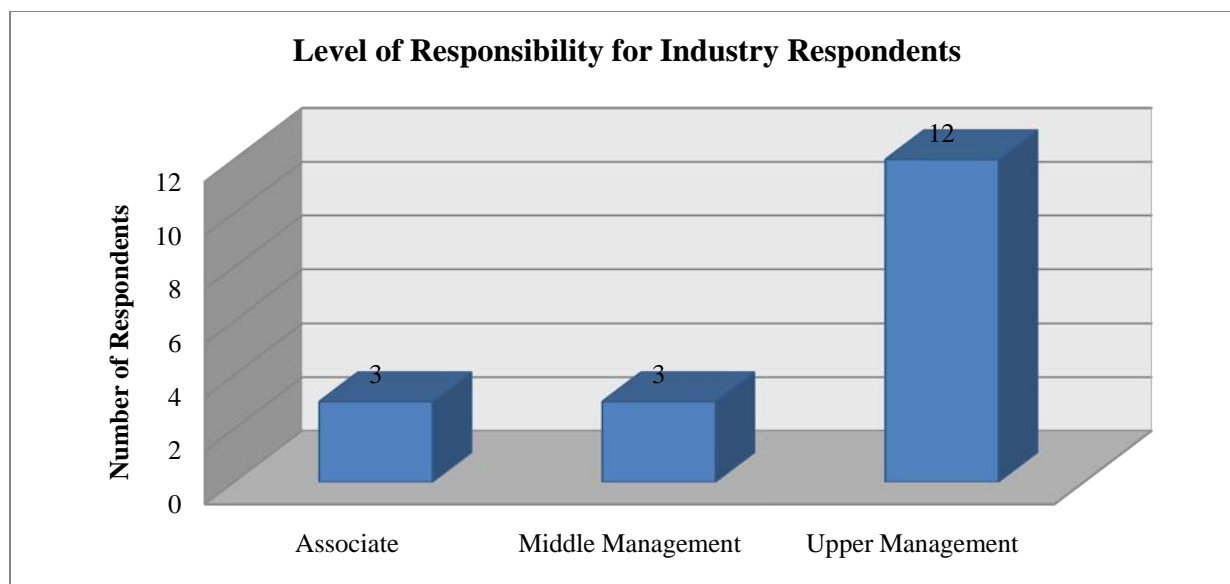


Figure 3 – Levels of Responsibility Within Their Firms for Industry Respondents

Guidance Document Usage

When asked about their thoughts on FDA Guidance Document utilization in the medical products industry, most industry respondents did not fluctuate on the types of Guidance Documents they had consulted in the past, the types they currently consult and the types they would most likely consult in the future. For example, those individuals who had utilized documents covering pre-marketing submission requirements in the past were likely using those same guidance documents currently and intended to continue to use them for the same types of issues in the future.

All eighteen industry respondents stated that they have used guidance documents in the past, currently use them and plan to continue using them in the future. Also, the resolution of Pre-Marketing Issues was the most common reason cited for utilization of guidance documents. In fact, 17 of the eighteen industry respondents stated that as a reason that guidance documents were used. All other reasons were given approximately 50-75% of the time. Figures 4, 5, and 6 depict how the industry respondents stated Guidance Documents were utilized.

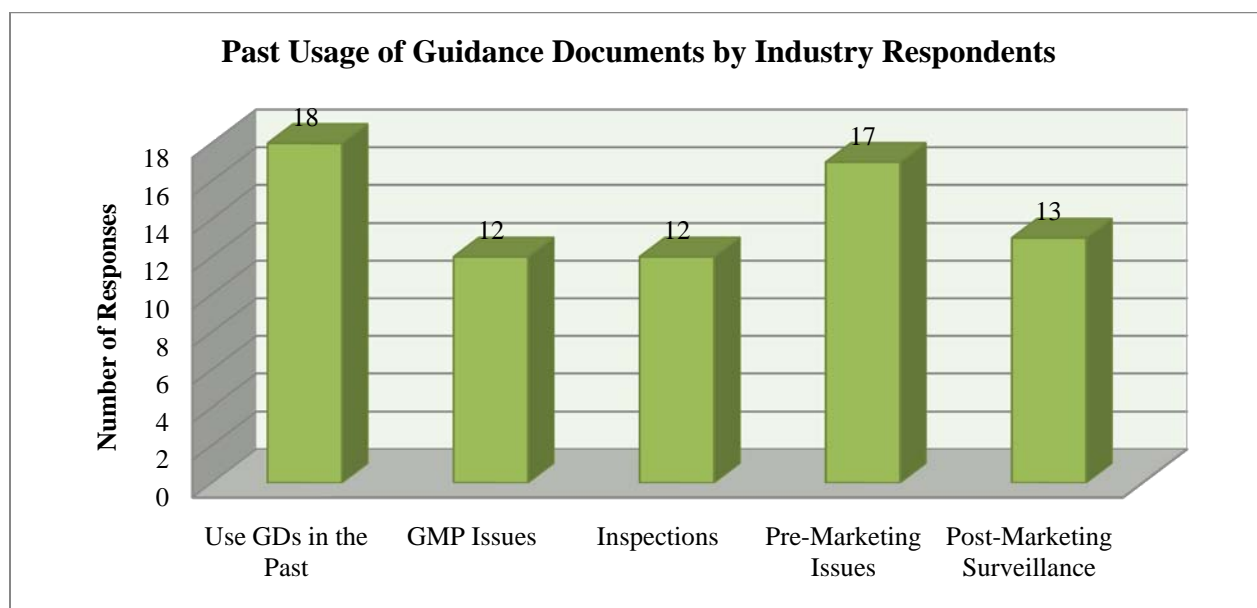


Figure 4 – Past Usage of FDA Guidance Documents by Industry Respondents

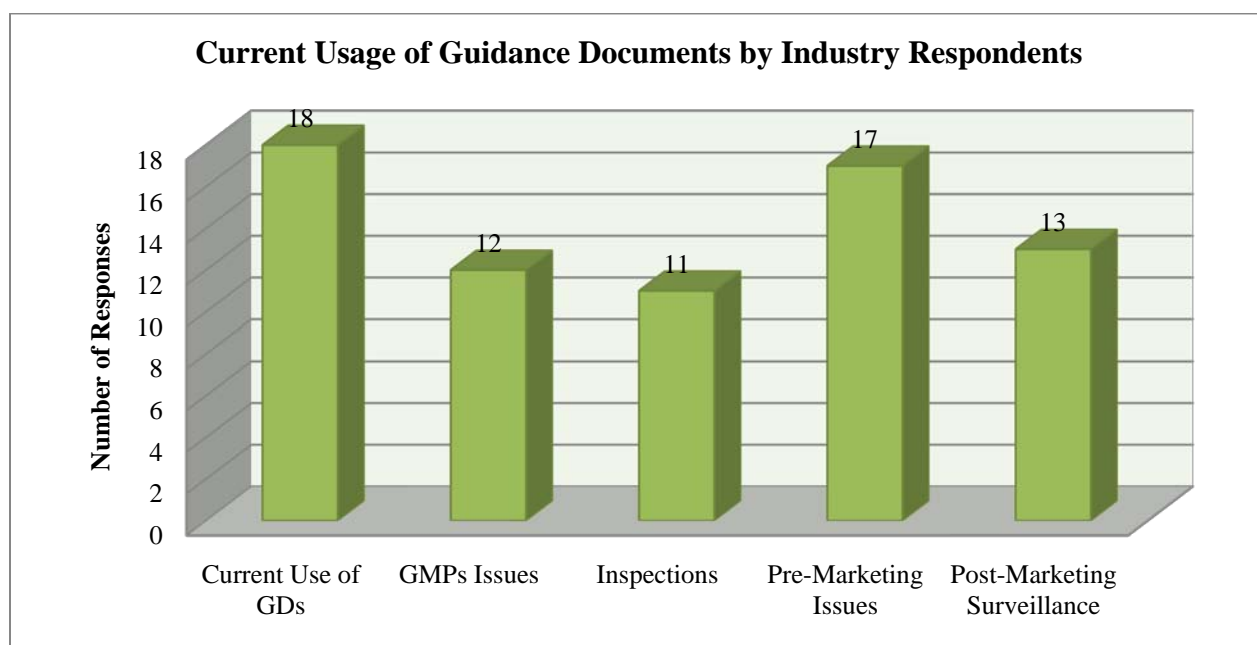


Figure 5 – Current Usage of FDA Guidance Documents by Industry Respondents

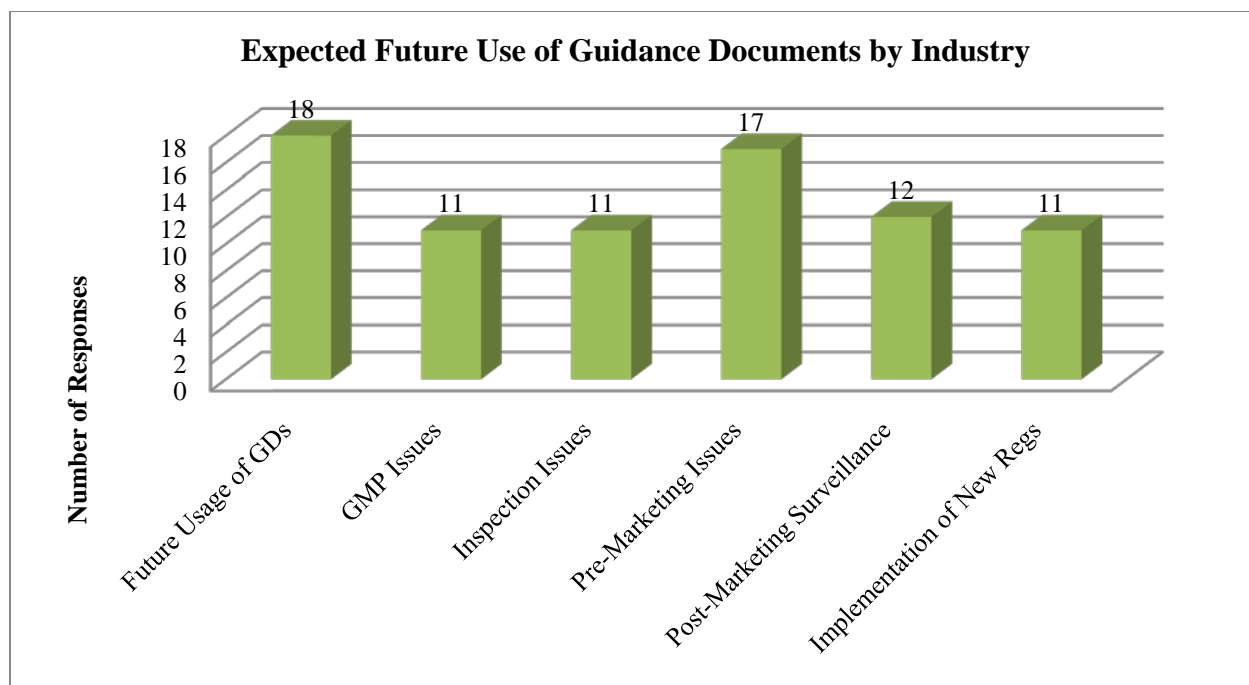


Figure 6 – Expected Future Usage of FDA Guidance Documents by Industry Respondents

When queried on the level of support and encouragement of management with regard to guidance document use, all but one of the eighteen industry respondents stated that the management of their companies encouraged their employees or clients to utilize FDA Guidance Documents in resolving medical product regulatory issues. The lone dissenter stated that the management of that particular firm did not find them useful for their particular product and further stated that management preferred to rely on its own interpretations of the regulations. Figure 7 depicts this overwhelming belief of management support of guidance document usage within the industry respondents' companies.

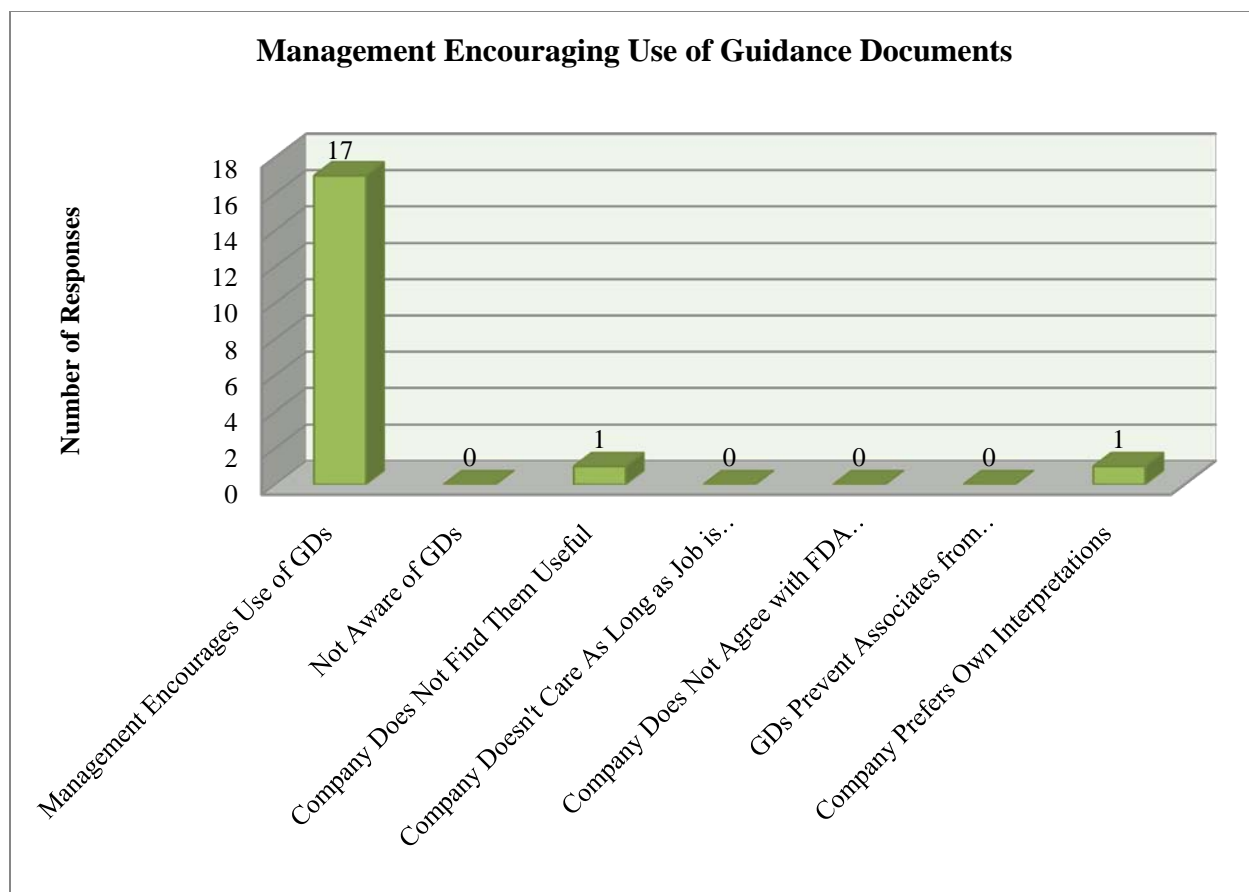


Figure 7 – Frequency of Management Encouraging the Use of Guidance Documents by their Employees

The Importance of Guidance Document Utilization

Many medical products industry personnel have strong opinions on what guidance documents mean to their industry and, by extension, to them. Title 21 Part 10.115(b) states that guidance documents “describe the agency’s interpretation of or policy on a regulatory issue”¹⁷, and it states that they “represent the agency’s current thinking”¹⁸ on regulatory matters. Sixteen of the eighteen industry respondents agreed that guidance documents were indeed useful in trying to understand the FDA’s current thinking on matters. One noted that there were too many guidance documents, and it was difficult to find one relevant to a specific situation. The final industry respondent stated that the guidance documents in place did not meet the specific needs

of his company. It should also be noted, however, that three industry respondents commented on the lack of timely response to requests for guidance and even questioned the use of the word “current” in describing guidance documents since many guidance documents took years to complete and implement beyond draft status, while other guidance documents were outdated and irrelevant. Figure 8 depicts the number of respondents who felt that guidance documents were useful in understanding the FDA’s current thinking on regulatory matters.

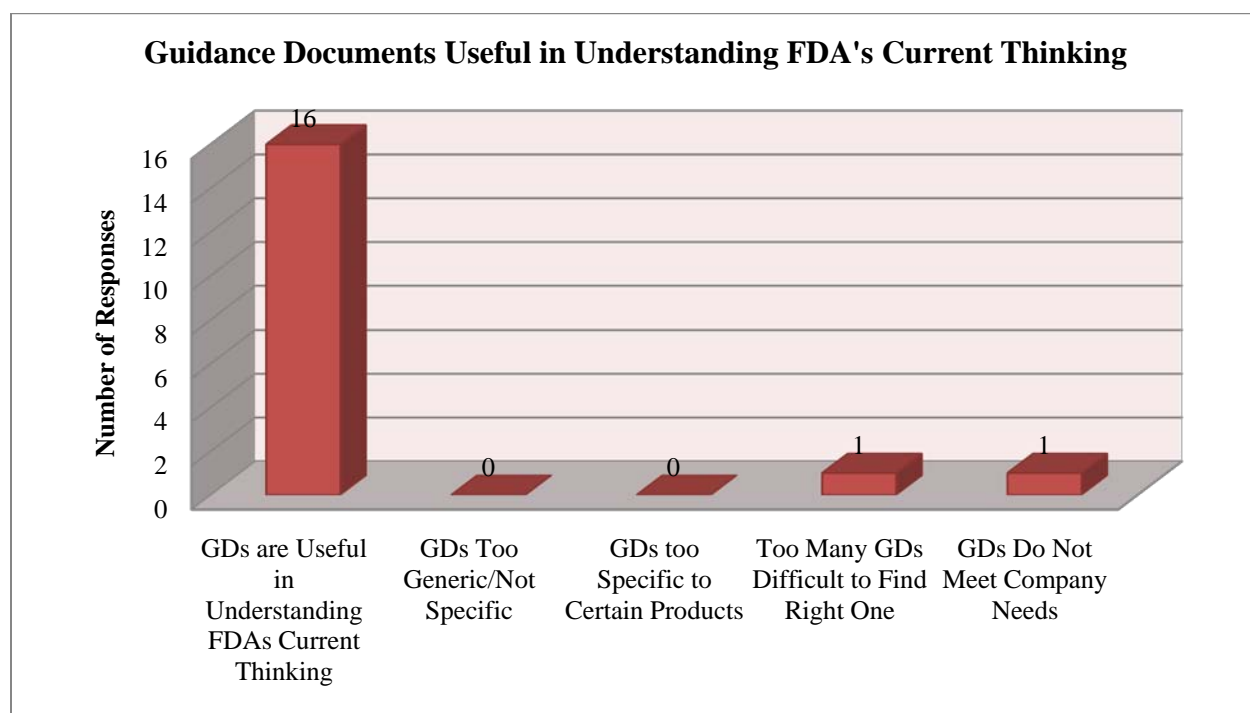


Figure 8 – Respondents Who Felt that Guidance Documents were Useful in Understanding the FDA’s Current Thinking on Regulatory Issues

While explaining the FDA’s interpretation of regulations in their guidance documents, it is important for the FDA to stay within the intended meanings of the laws and regulations being explained since, although not legally binding, guidance documents were viewed by four medical products industry respondents as being equivalent to a law. Another four respondents from the

medical products industry implemented guidance document recommendations almost as though they were law in order to stay ‘off of the FDA’s radar’, so to speak. Of the remaining ten respondents, six implemented the most critical ones and the last four viewed guidance documents as suggestions which were implemented only if they made the most sense for the respondent’s business processes. Figure 9 depicts the industry respondents split opinions on how guidance documents were viewed and treated at their companies.

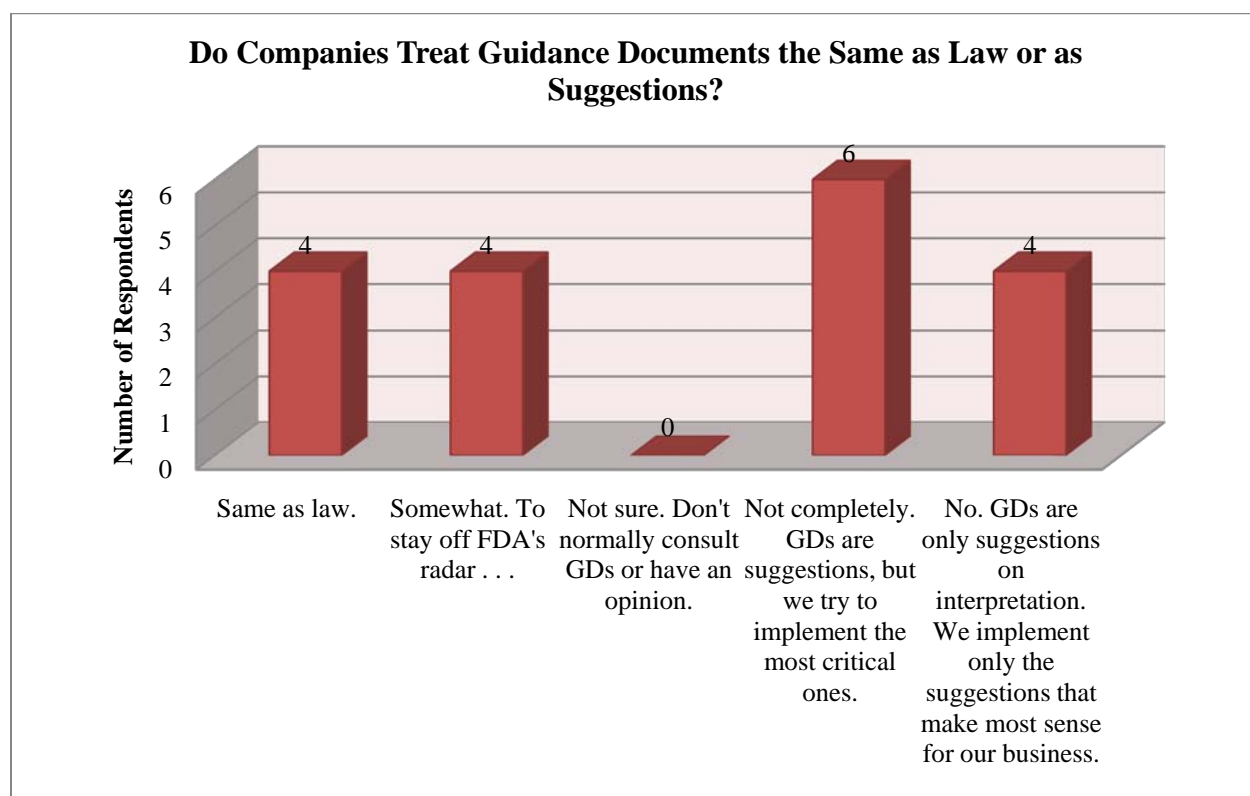


Figure 9 – Industry Respondent Opinions on How Guidance Documents were Viewed and Treated by their Companies

One would think that given the tendency of a substantial portion of the members of the medical products industry to treat guidance documents like law or nearly like law, the FDA would be sure to develop and implement guidance documents that closely followed the intended

meanings of the regulations. Indeed, nearly all industry respondents felt that the FDA did a good job of ensuring that most guidance documents fell within the intended meanings of the laws and regulations they were explaining, as depicted in Figure 10. In fact, eleven of the eighteen respondents replied that guidance documents followed the intended meanings of the regulations, while six more stated that guidance documents mostly followed the intended meanings. This means that, in general, a large majority of the respondents felt that the FDA was successful in creating guidance documents that were representative of the regulations they were attempting to explain.

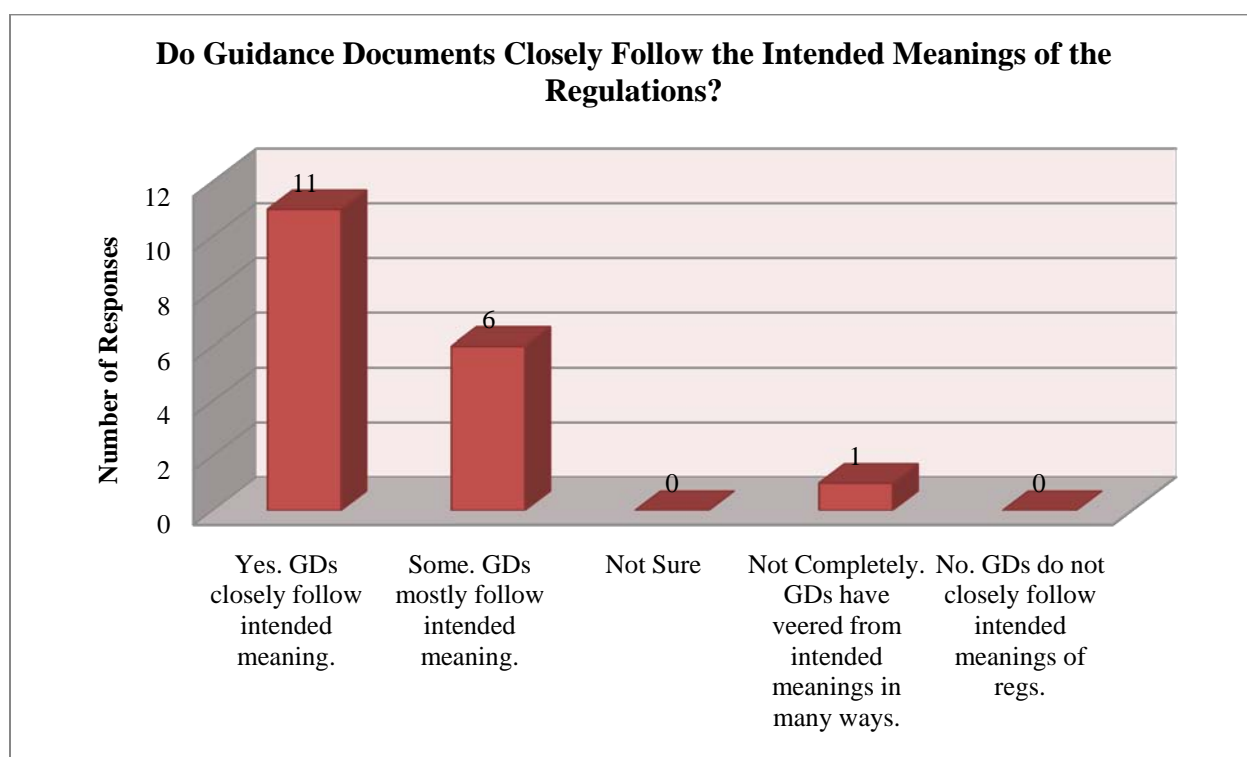


Figure 10 – Industry Respondents Who Felt that Guidance Documents Followed the Intended Meanings of the Laws and Regulations

Although most industry respondents indicated they felt that FDA Guidance Documents did a good job of following the intended meanings of the regulations, several of them also felt

that, at times, it was appropriate to utilize guidance documents in testing out potential new regulations before going through the trouble of trying to implement them as regulations. Of note was the strength of opinions on this particular topic. The five respondents who answered “yes” seemed reasonably non-committal about it with responses such as “That is not a bad idea” or “Sure. That makes sense, I suppose.” Another four respondents were even more non-committal when they answered “somewhat, as long as the spirit of the regulations is maintained”. However, the ten respondents who answered “No” to this question were, in general, much more emphatic about their responses by stating “Absolutely not!” or “That is not appropriate!” Although two of them liked the concept of testing regulations, they did not think guidance documents were the correct medium for these tests. Figure 11 depicts how willing industry respondents were to allow the FDA to test potential new regulations via guidance documents.

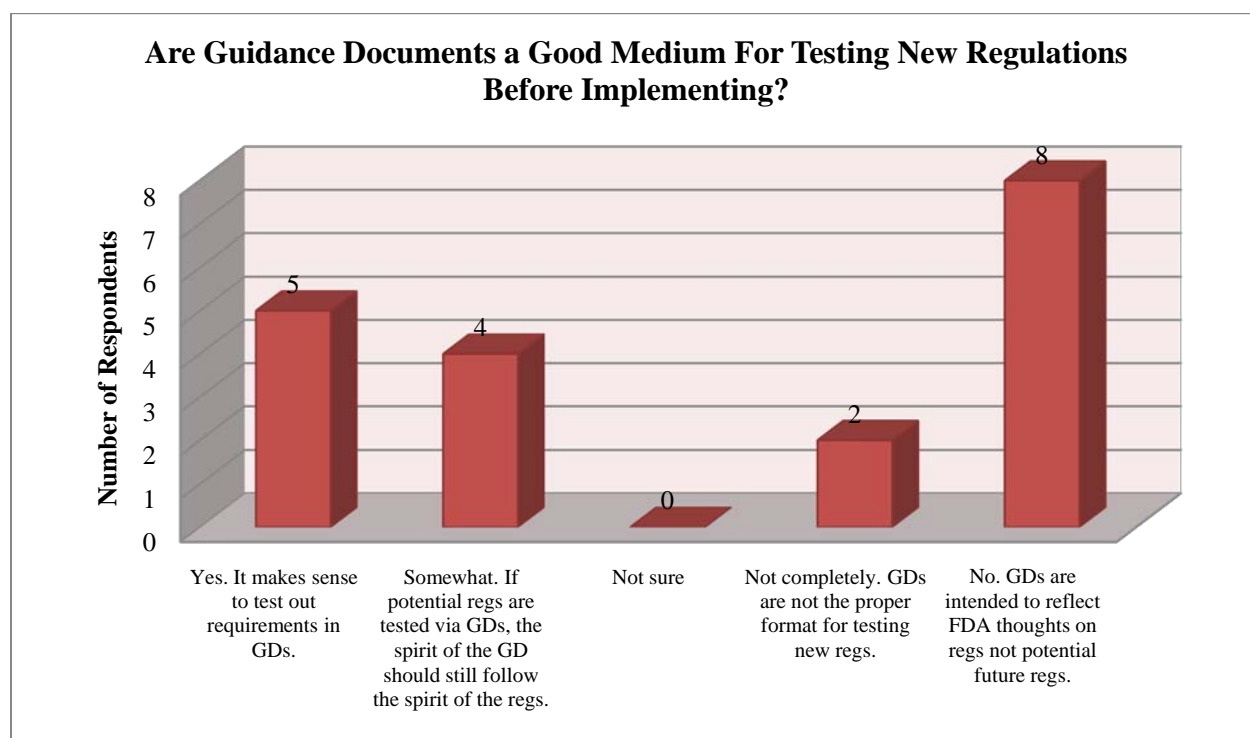


Figure 11 – Industry Respondent Opinions on Using Guidance Documents to Test Potential New Regulations Prior to Implementing Them

As previously stated, guidance documents are intended to “describe the agency’s interpretation of or policy on a regulatory issue”¹⁷. However, it is important to understand the ultimate impact of guidance documents on the medical products being produced and sold. When asked about whether they felt that guidance documents helped the medical products industry produce safer and more effective products, the results indicated that thirteen out of eighteen respondents felt guidance documents positively impacted safety and effectiveness. The industry respondents who answered “no” to this question explained their answer by stating that guidance documents simply helped the industry maintain compliance; they did not necessarily make a noticeable impact on the safety or effectiveness of the product like a product’s design would. Figure 12 depicts the industry responses to whether or not guidance documents helped the industry produce safer and more effective products.

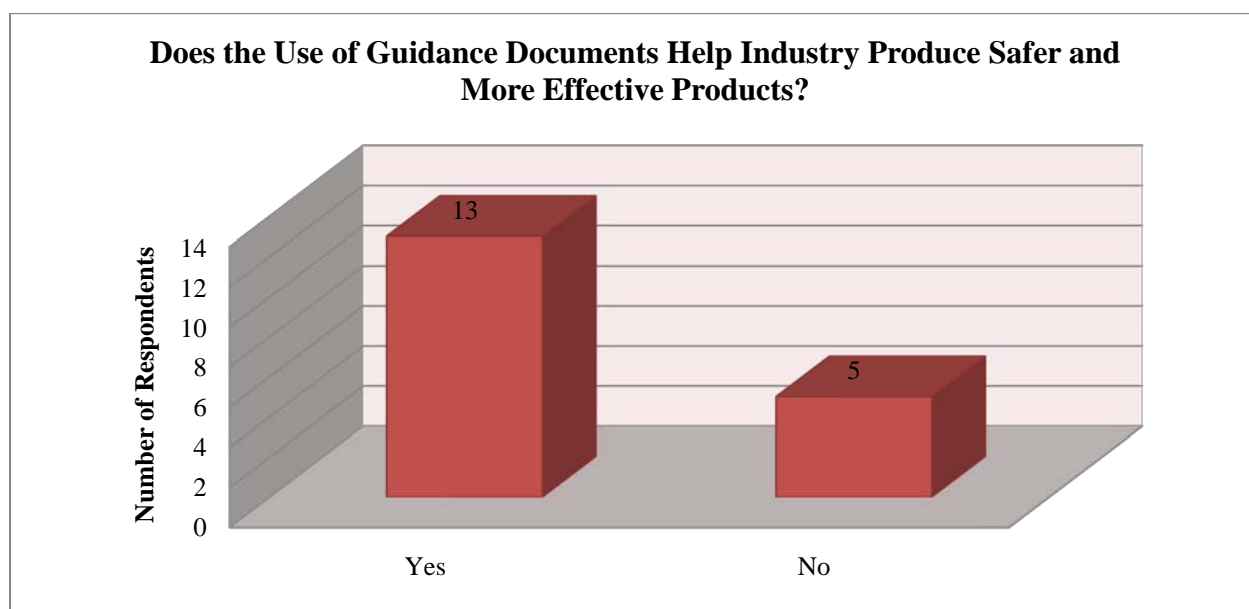


Figure 12 – Industry Respondent Opinions on Whether or Not Guidance Documents Helped Produce Safer and More Effective Products

As previously established, one of the key uses of guidance documents is to help the industry achieve and maintain compliance with the regulations. When queried if they felt as though guidance documents were an effective tool for this, industry respondents overwhelmingly stated that guidance documents were effective compliance tools, as depicted in Figure 13. Sixteen of the eighteen respondents answered that guidance documents were effective regulatory tools for achieving and maintaining compliance. An additional respondent replied “yes” but felt that additional features could make them more effective. The final respondent felt that guidance documents were not effective tools for achieving compliance because there were too many of them to choose from, which causes confusion, and there were too many that were out of date and irrelevant.

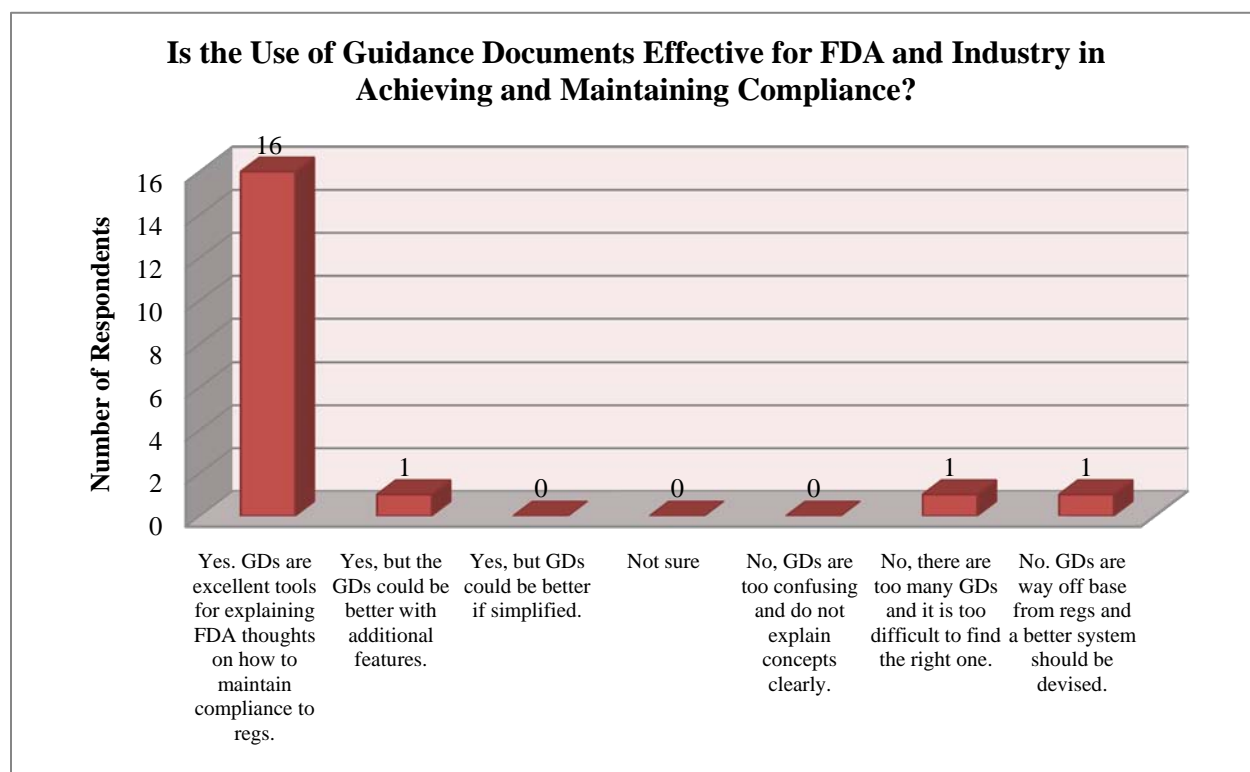


Figure 13 – Industry Respondent Opinions on Guidance Documents as Compliance Tools

Supplementing Guidance Documents

To supplement the use of guidance documents in industry, the industry respondents also stated that many of them followed-up on regulatory issues after consulting guidance documents by contacting either the FDA or regulatory consultants to clarify the FDA's thoughts and opinions or to verify that the thoughts explained in the guidance document were still current and relevant. Fourteen of the eighteen industry respondents stated they occasionally contacted consultants. However, only eleven of them stated they occasionally contacted the FDA. Figure 14 depicts the frequency at which industry respondents contacted the FDA and consultants to clarify or verify the content of guidance documents. Figure 15 depicts the centers most often contacted by the industry respondents.

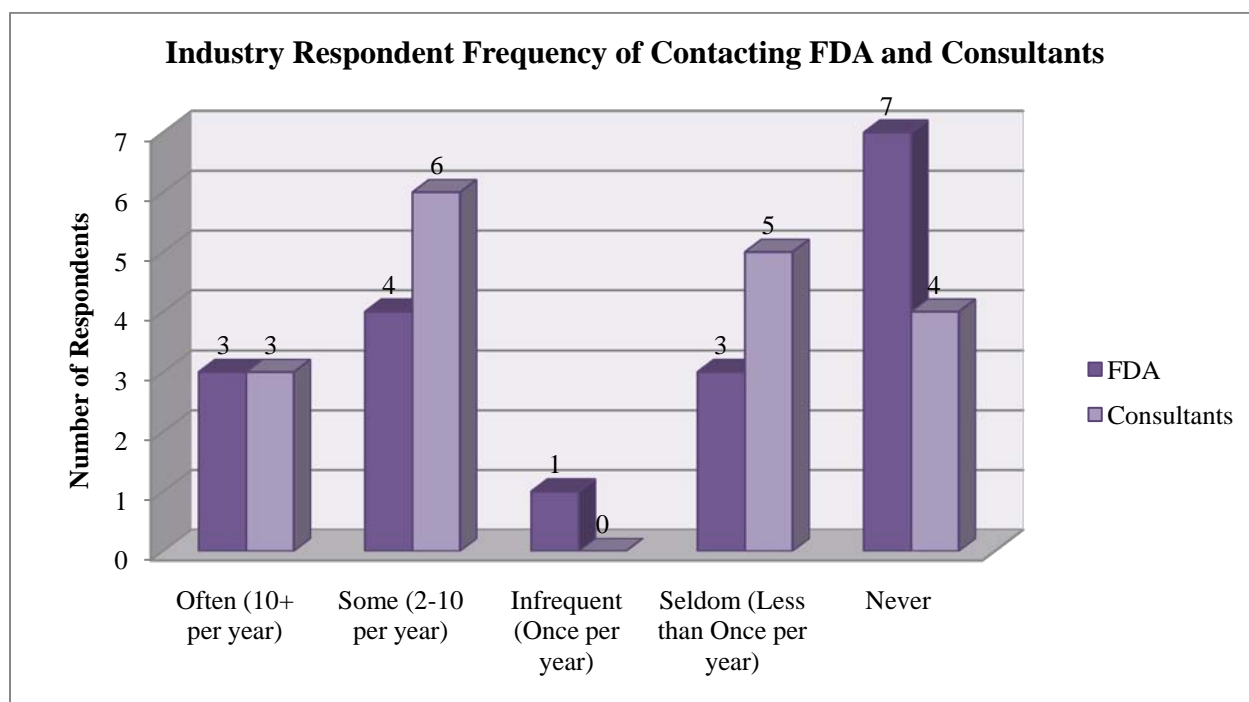


Figure 14 - Industry Respondent Frequency of Contacting FDA and Consultants for Guidance Document Clarification

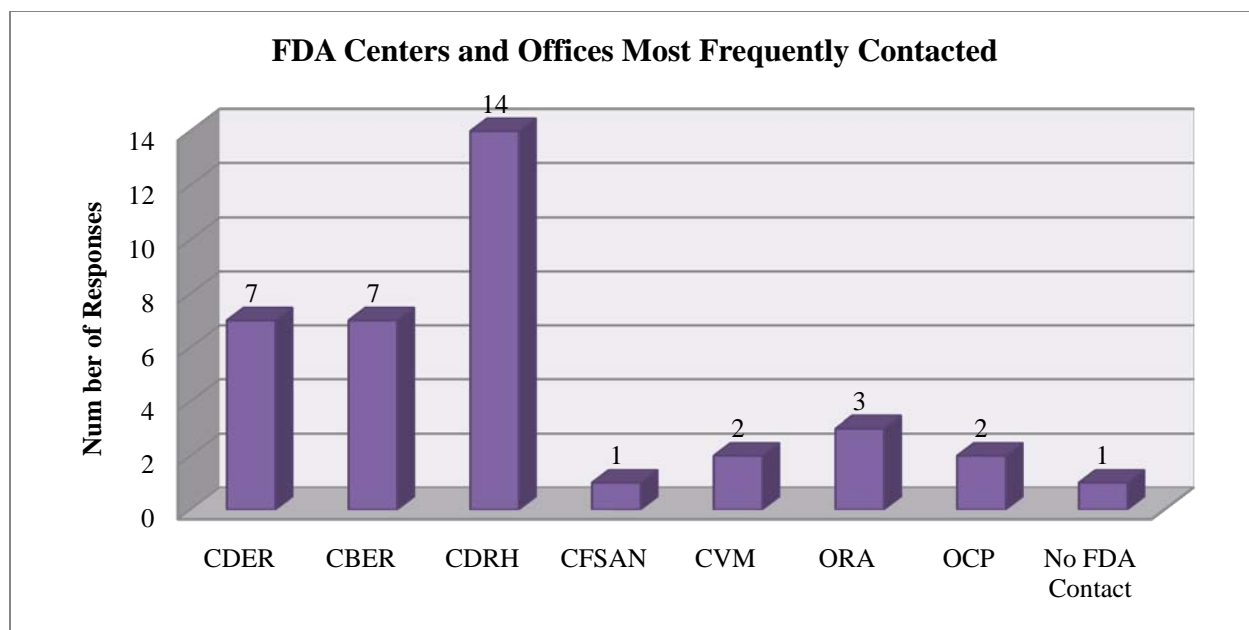


Figure 15 – FDA Centers Most Frequently Contacted by Industry Respondents for Clarification or Verification of Guidance Document Currency – Note: CDER = Center for Drug Evaluation and Research, CBER = Center for Biologics Evaluation and Research, CDRH = Center for Devices and Radiological Health, CFSAN = Center for Food Safety and Applied Nutrition, CVM = Center for Veterinary Medicine, ORA = Office of Regulatory Affairs, OCP = Office of Combination Products.

Of the seven industry respondents who had used guidance documents from multiple FDA centers, four respondents stated that the Center for Devices and Radiological Health (CDRH) produced the best and most effective guidance documents in terms of overall document quality and availability of desired documents. The Center for Drug Evaluation and Research (CDER) and the Center for Food Safety and Applied Nutrition (CFSAN) guidance documents were also commented on as reasonably effective by one of the respondents. Two different industry respondents specifically pointed out that the Center for Veterinary Medicine (CVM) and the Center for Biologics Evaluation and Research (CBER) were both deficient in their guidance documentation as compared to the other centers in terms of both the content of existing documents as well as the availability of documents. 70% of the industry respondents had no

opinion because they had either not worked with guidance documents from multiple areas, or they did not feel the different centers' documents were comparable since their approaches and subject matters were so vastly different. Figure 16 depicts the industry respondent opinions on which FDA center had the best guidance documents.

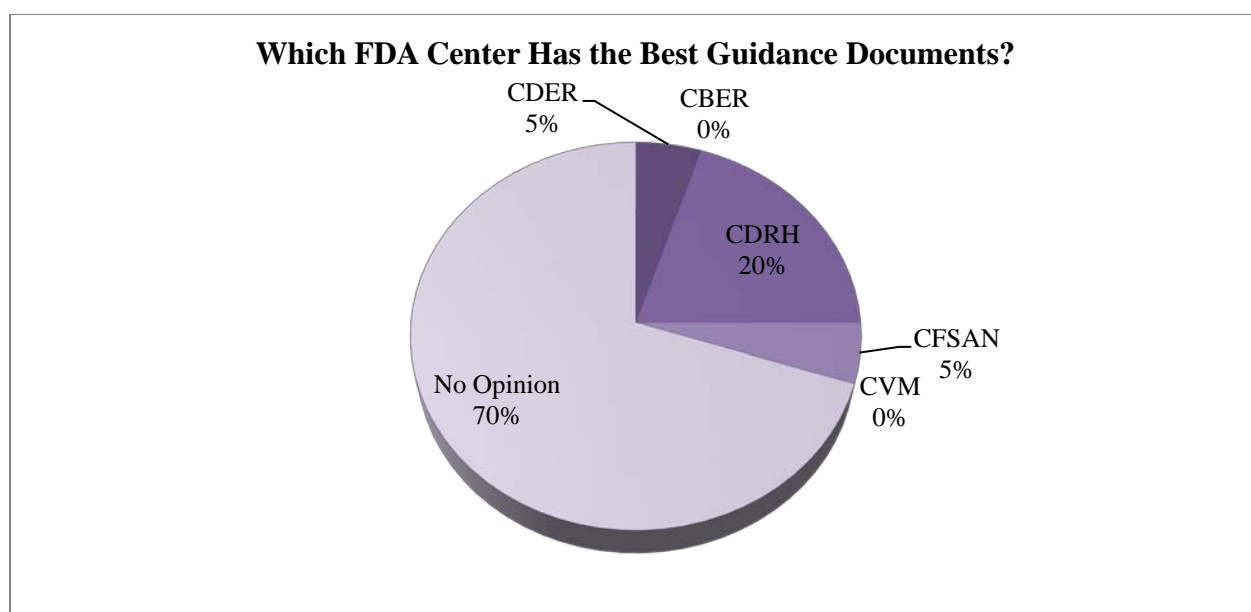


Figure 16 – Industry Respondent Opinions on Which FDA Center had the Best Guidance Documents

Potential Negative Impacts of Guidance Document Usage

It is important to note that not all impacts felt by the use of guidance documents are considered positive. For example, there is a risk of becoming overly dependent on guidance documents for making regulatory decisions within the company. A result of such over-dependence could be the creation of a quality system that is essentially compliant with regulations but does not meet the specific needs of the company. In this type of situation, where the quality system does not meet the needs of the company, the risk is much higher that

employees will have to develop work-arounds and look for loop-holes in order to maintain productivity in an inefficient quality system.

Industry respondents were asked their opinion on whether there is a legitimate concern for over-dependence on guidance documents to cause companies to implement FDA recommendations without attempting to understand the regulations for themselves. As depicted in Figure 17, fourteen of the eighteen industry respondents did not agree this was a legitimate concern. Two respondents stated that a competent regulatory affairs manager would make decisions based on all available information and not just one or two sources. However, that does not alleviate the risk if such a situation were to occur.

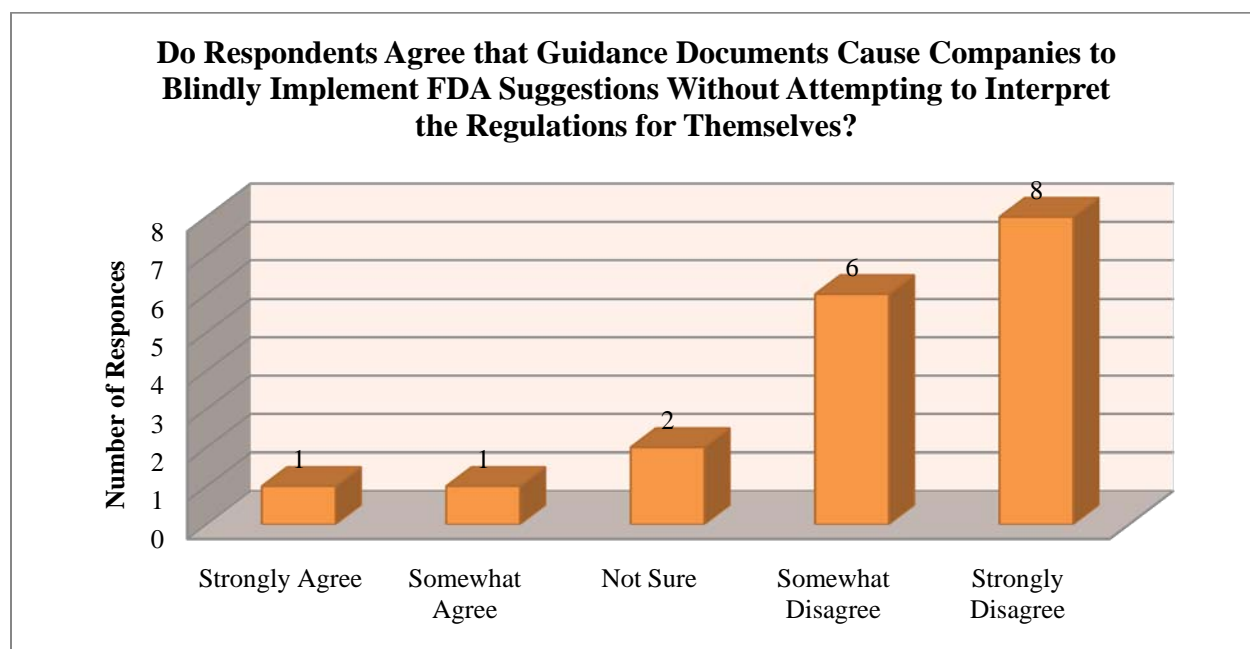


Figure 17 – Industry Respondent Opinions on Whether Guidance Documents Made Regulatory Affairs Personnel More Likely to Not Attempt to Understand the Regulations for Themselves

Another risk with using guidance documents is that the FDA may become too dependent on them. One could argue that this is a possible explanation for the case of *United States v. Utah*

Medical Products, Inc. where, as previously discussed, an FDA inspector cited a company for noncompliance to a guidance document. Although guidance documents are not legally binding to the FDA, the regulations do state that “FDA employees may depart from guidance documents only with appropriate justification and supervisory concurrence”¹⁸. When asked if any of the industry respondents had experienced a situation in which an FDA inspector had cited a company for nonconformance to a guidance document but which was not strictly required by the regulations, thirteen respondents said this had never happened, and three respondents went on to explain how supervisory oversight and the TurboEIR program used by many FDA inspectors prevented such mistakes. The TurboEIR program is an electronic report-making program whose use is encouraged by FDA management in creating “accurate, consistent, and complete” Establishment Inspection Reports¹⁹. Alternatively, when queried about whether they were aware of a situation in which an FDA product reviewer had held up a product approval or clearance due to noncompliance with a guidance document, twelve of the respondents replied that they were aware of this type of situation occurring at either their company or a previous employer. Figures 18 and 19 depict industry respondents’ comments on FDA’s enforcement activities with regard to guidance documents.

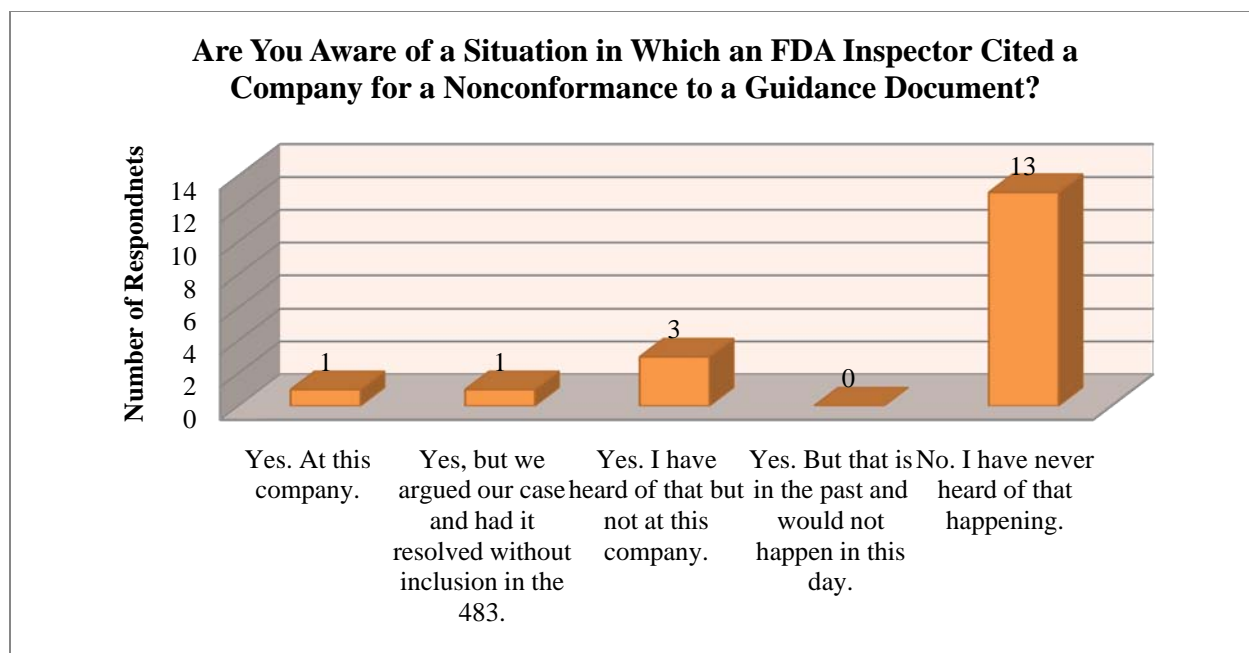


Figure 18 – Industry Respondents Aware of FDA Inspectors Citing Nonconformances to Guidance Documents

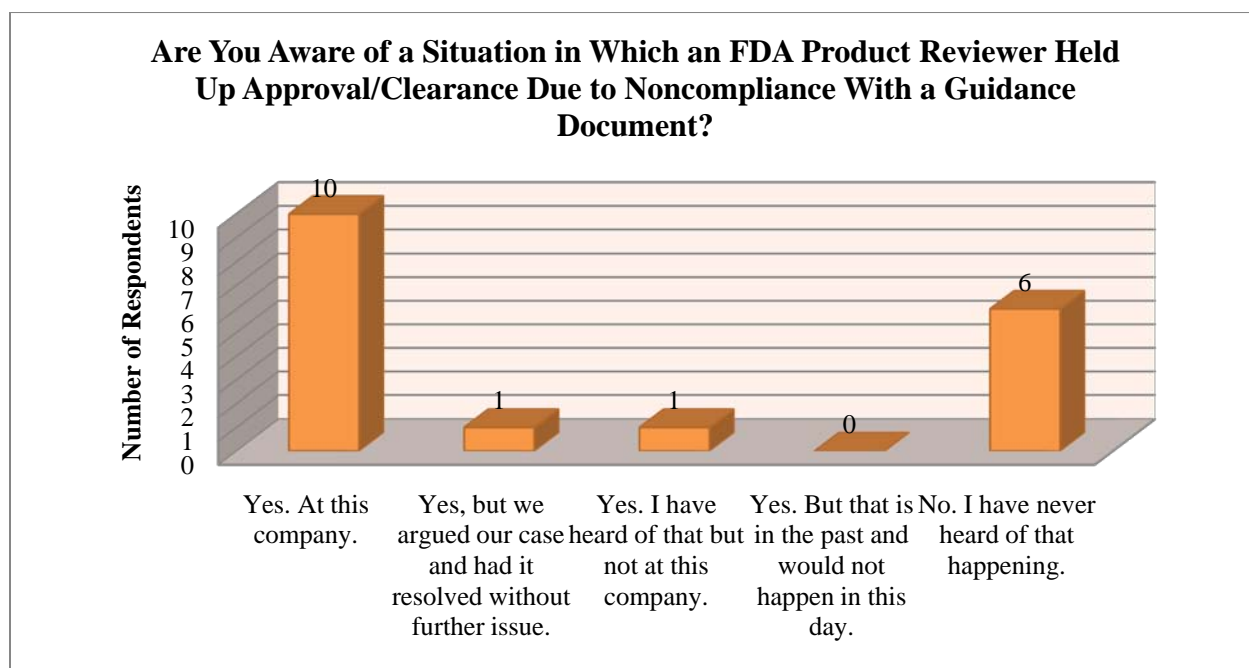


Figure 19 - Industry Respondents Aware of FDA Reviewers Holding Up New Product Approvals/Clearances for Nonconformances to Guidance Documents

Improving Guidance Documents

As discussed previously, new and revised guidance documents undergo a period of public review and commenting. During this time, comments are collected and reviewed by the FDA to determine if their interpretations are synchronized with the industry's expectations. Of the eighteen industry respondents, eleven of them had commented on at least one draft guidance document. In addition, eight of those individuals felt as though the FDA gave their comments serious consideration with regard to development of the final guidance document. Figure 20 depicts this data.

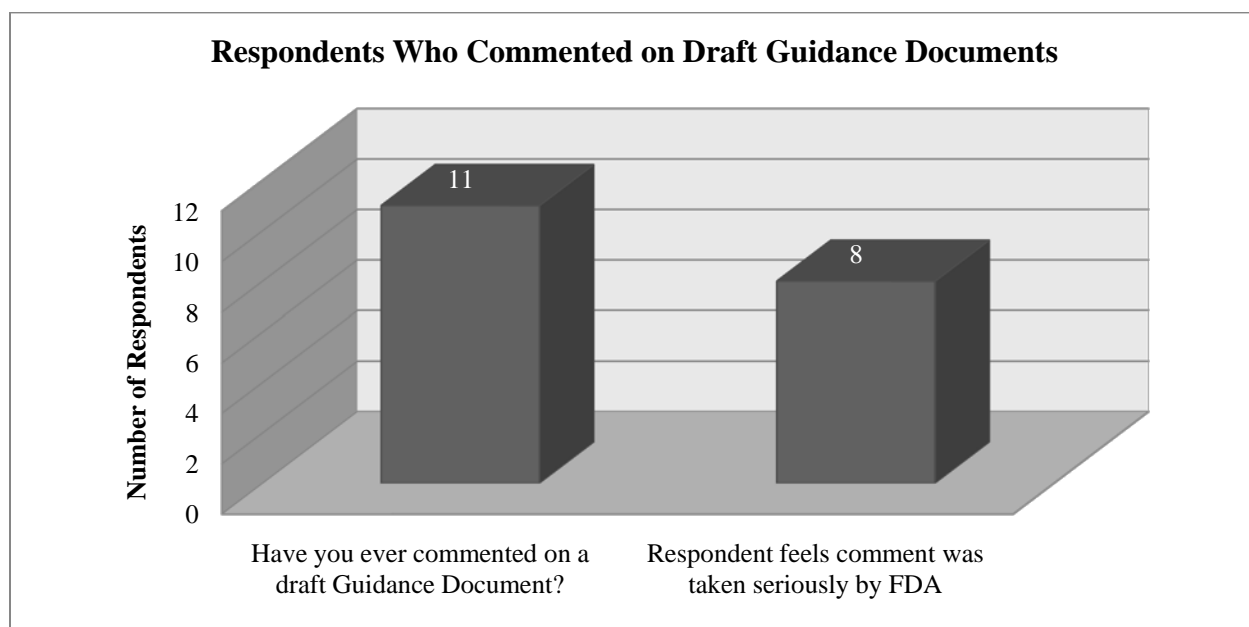


Figure 20 – Industry Respondents Who Had Commented on Draft Guidance Documents and Their Opinions on How Seriously the FDA Considered Their Comments

In terms of improving the guidance document system as a whole, the majority of industry respondents felt that guidance documents were a reasonably effective method for providing guidance to regulated industries. However, only four industry respondents stated the system was acceptable as implemented with no recommended changes. The most significant shortcoming in

the system was the length of time required to publish a final guidance document. Thirteen of the eighteen industry respondents identified this as an area in need of improvement. With technological advances progressing at current rates and new applications of technology in the medical products industry constantly being developed, industry respondents felt the guidance document system was currently unable to meet industry demands. Efforts need to be made to streamline this process and make it more efficient so that guidance documents are available quicker. Ideally, this would provide medical products companies with the necessary guidance documents at the time of their new product submission, which should help smooth the submission process and allow products to get to the market with the proper clearances and approvals much quicker. Figure 21 depicts industry respondent feelings with regard to necessary changes to the guidance document system.

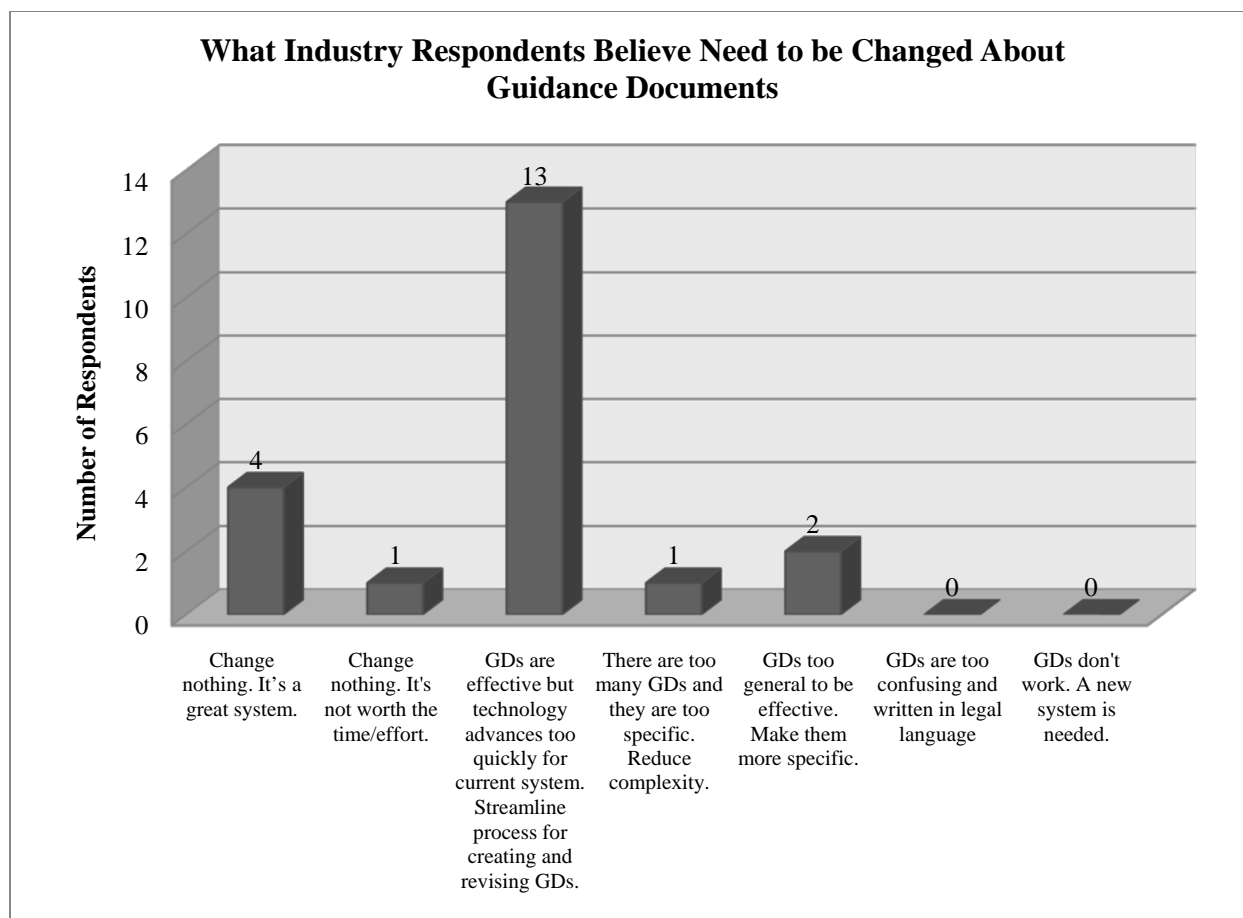


Figure 21 – Industry Respondent Opinions on Necessary Changes to the Guidance Document System

When asked what their vision of a new system for the FDA to use to provide guidance to the medical products industry might look like, the industry respondents provided a wide variety of responses. Two of them stated they would make better use of technology to develop a web-based Wiki system, which is a collaborative effort of collecting and presenting information. In this type of system, FDA personnel, industry representatives and other interested parties could all log in and have a chance to shape the development of new guidance documents. This could potentially have a major impact on how quickly guidance documents are created because the process of commenting on the document happens concurrently with the writing of the document.

As with any Wiki system, however, the ability to control access to the system needs to be thoroughly considered.

Other suggestions from industry respondents include having more examples, as well as better and more up-to-date examples; make more efforts to harmonize guidance documents with the ISO, ICH and other international standards; and narrow the scope of guidance documents and make them more specific by product type while adding a statement of scope that specifies when the guidance document does not apply.

CHAPTER 4

FDA RESPONSES

Demographics of FDA Respondents

Although a large number of FDA personnel were contacted for the purposes of this research, only eight people agreed to participate. The primary reason given for not participating was a reluctance to give interviews without permission from a supervisor or from the FDA's Press Office. However, for the most part, opinions were similar enough from respondent to respondent to make some general observations about the population even though the sample population was smaller than the desired sample size of 25.

The average number of years the FDA respondents had worked in the medical products industry was 29.9 years with a total range of 25 to 40 years. Three of the FDA respondents were from field offices, and five were from FDA headquarters. Figure 22 depicts the FDA respondents' areas of expertise. Similar to the industry respondents, the FDA respondents were skewed towards medical devices with seven respondents. Three respondents had expertise in pharmaceuticals. One respondent had expertise in veterinary products, and the final one was an expert in the creation and revision of guidance documents. Note that, like the industry respondents, many of the FDA respondents had multiple areas of expertise.

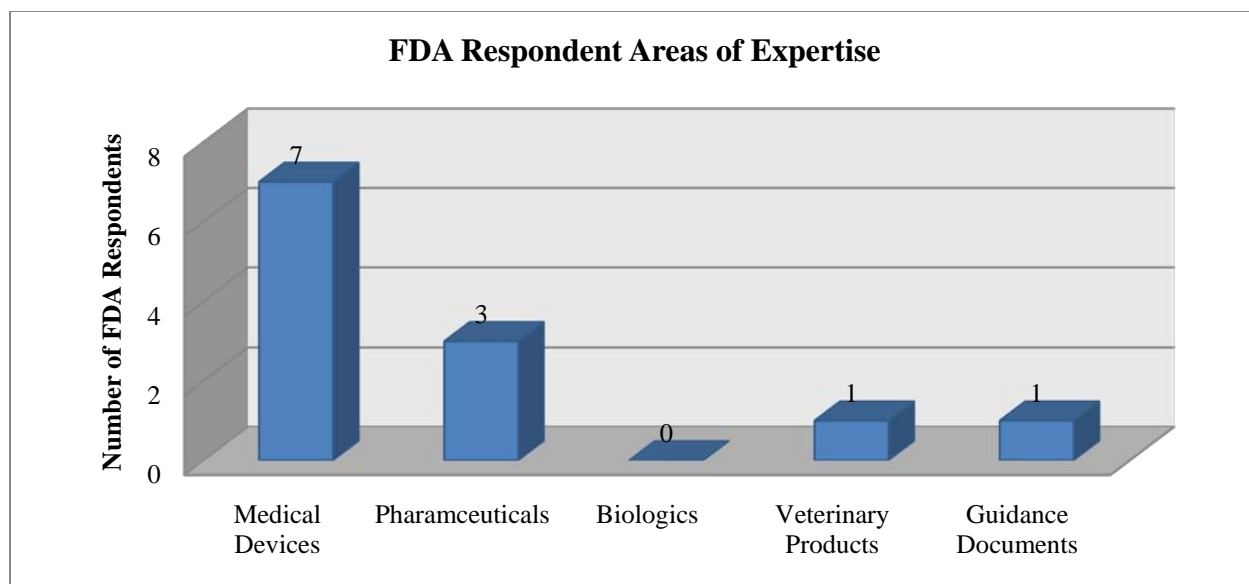


Figure 22 – FDA Respondent Areas of Expertise

In addition to having varying backgrounds and extensive experience with the FDA, the respondents were also in positions of varying levels of responsibility. As depicted in Figure 23, there was a broad range of responsibility levels in the FDA respondents. Four respondents were at the associate level; one was considered middle management; and the final three respondents were considered upper management.

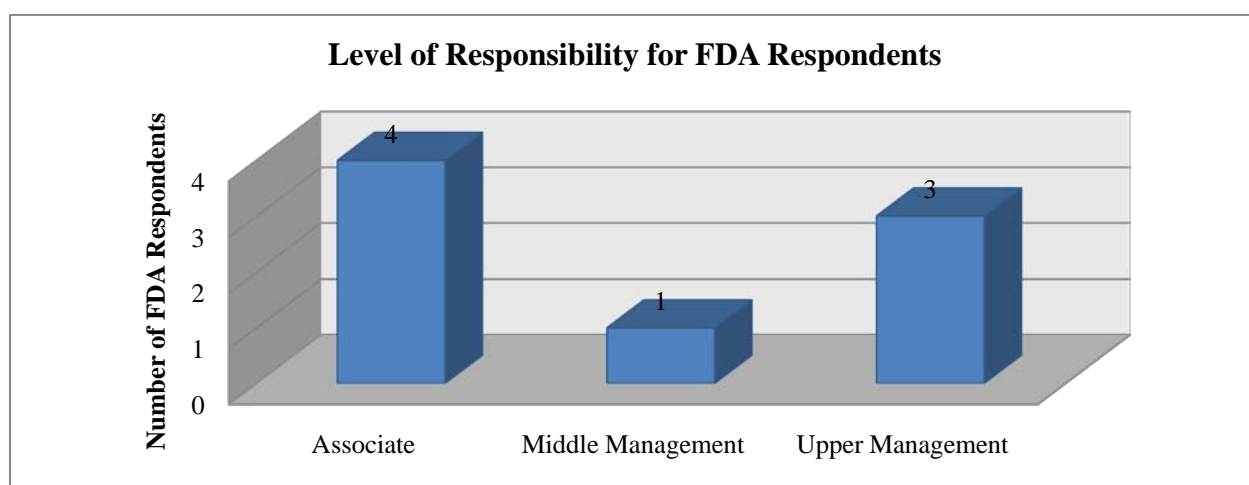


Figure 23 – Levels of Responsibility for FDA Respondents

Guidance Document Usage

When asked to give their observations about guidance document usage in industry in the past, present and future, just as with the industry respondents, there was little or no fluctuation by any individual from one time frame to the next. Figures 24, 25, and 26 depict FDA respondent observations of guidance document usage and expected usage by industry across the past, present and future. Note that these charts are very similar to Figures 4, 5, and 6, which depict the same thing from the industry respondents' points of view. The similarities of these two sets of charts demonstrate a common set of opinions between the two groups with regard to guidance document usage.

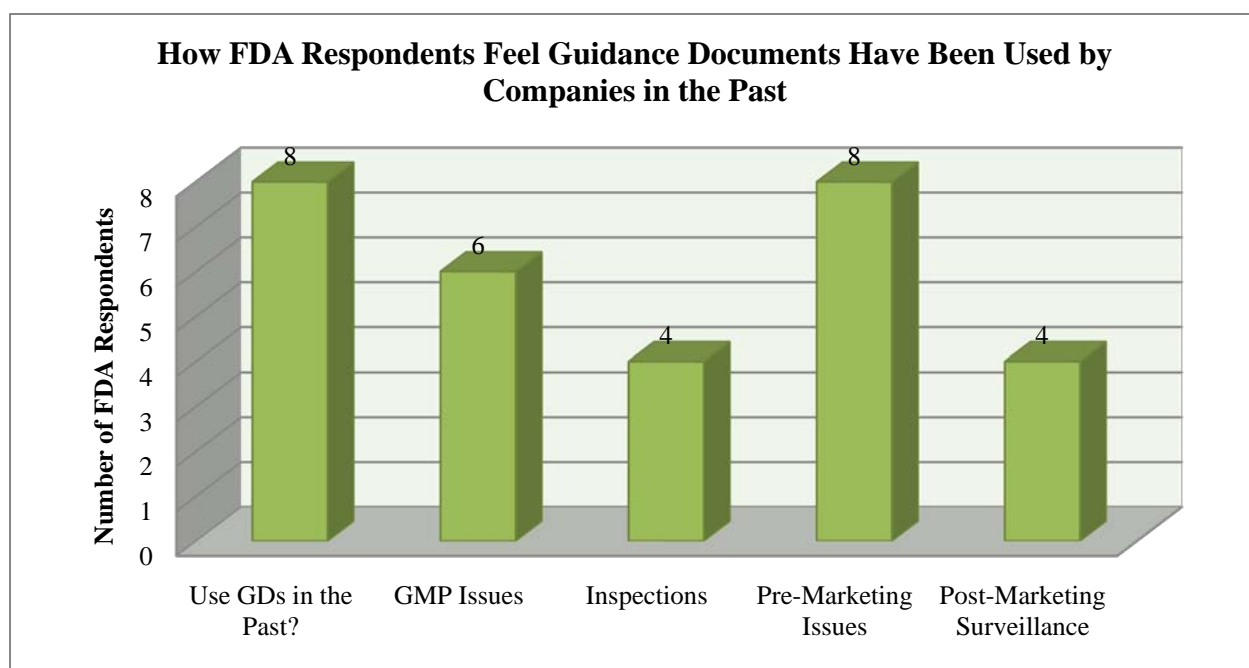


Figure 24 – Past Usage of Guidance Documents by Industry as Observed by FDA Respondents

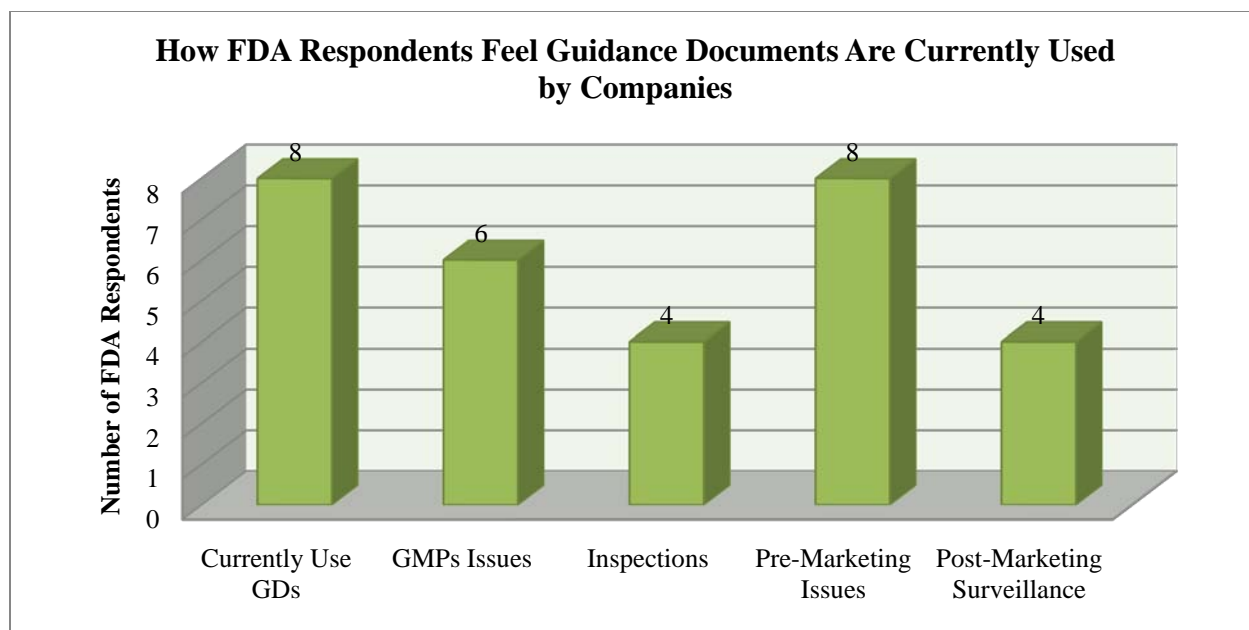


Figure 25 – Current Usage of Guidance Documents by Industry as Observed by FDA Respondents

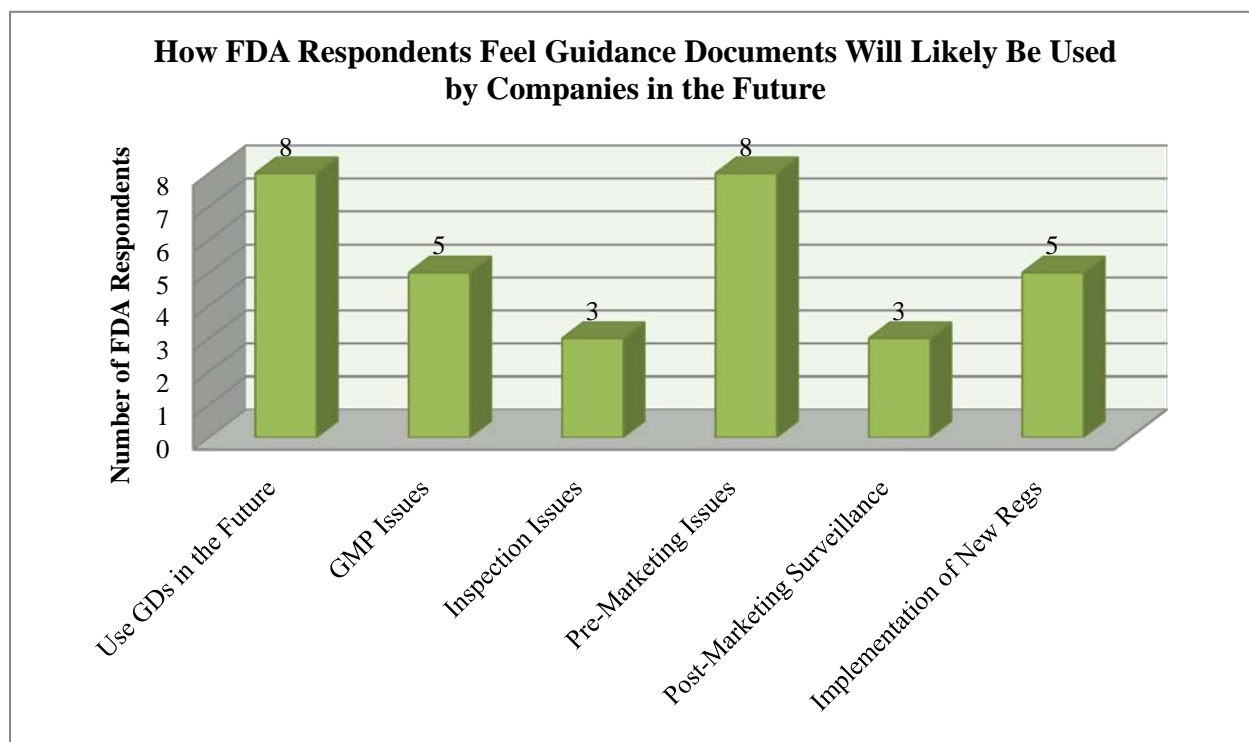


Figure 26 – Expected Future Usage of Guidance Documents by Industry as Observed by FDA Respondents

Figure 27 depicts FDA respondents' thoughts on FDA management's encouragement for the utilization of guidance documents. The unanimous opinion that FDA management supports guidance document usage is not surprising given the regulatory mandate within the GGP's for FDA employees to use guidance documents unless they have "appropriate justification and supervisory concurrence"¹⁸ for not using them.

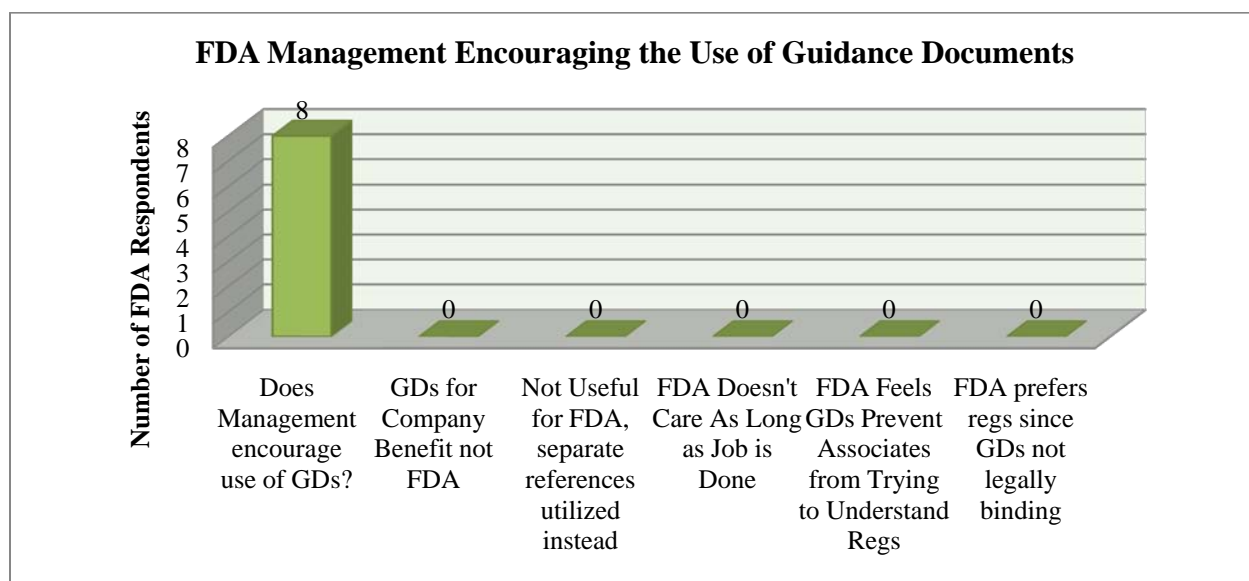


Figure 27 – FDA Management Encouraging the Use of Guidance Documents

The Importance of Guidance Document Utilization

As is the case with industry respondents, the FDA respondents also had strong opinions on what guidance documents meant to them and to the medical products industry. Previous chapters discussed, in depth, the intent of the guidance documents to “represent the agency’s current thinking”¹⁸ on regulatory matters. When queried on this matter, all eight of the FDA respondents, like the industry respondents, stated that guidance documents were generally successful in conveying the agency’s current thoughts and interpretations on regulations, as depicted in Figure 28. Two of them acknowledged that many guidance documents were out of

date and that new documents took too long to create and publish. One FDA respondent mentioned several times how unfunded mandates and additional responsibilities bestowed upon the FDA over the years had taken a toll on the FDA's ability to complete tasks quickly or efficiently.

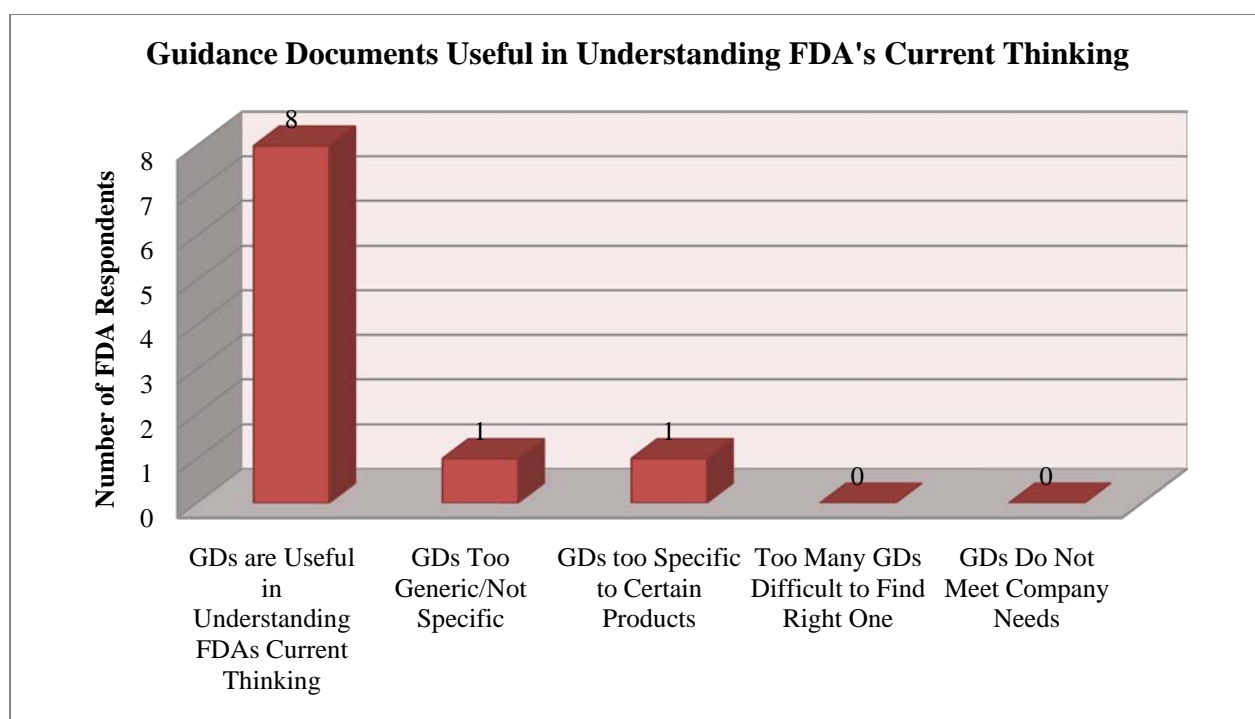


Figure 28 – FDA Respondents Who Felt that Guidance Documents were Useful in Understanding the FDA's Current Thinking on Regulatory Issues

Probably because they are mandated by regulations to use them, FDA respondents were nearly unanimous in viewing guidance documents as equivalent to laws. Industry respondents, as depicted previously in Figure 9, were much more diverse in their opinions of whether guidance documents are treated the same as law, since their responses were almost evenly split between positive and negative answers. However, by contrast, five of the eight FDA respondents responded that, in their opinion, industry considered these to be equivalent to laws or regulations while two more considered them to be somewhat equivalent to laws. Although these opinions are

understandable, it still is disturbing since it implies that FDA personnel hold guidance document contents to the same level of importance as the regulations. Figure 29 depicts FDA respondent opinions on whether the industry viewed guidance documents as being equivalent to laws.

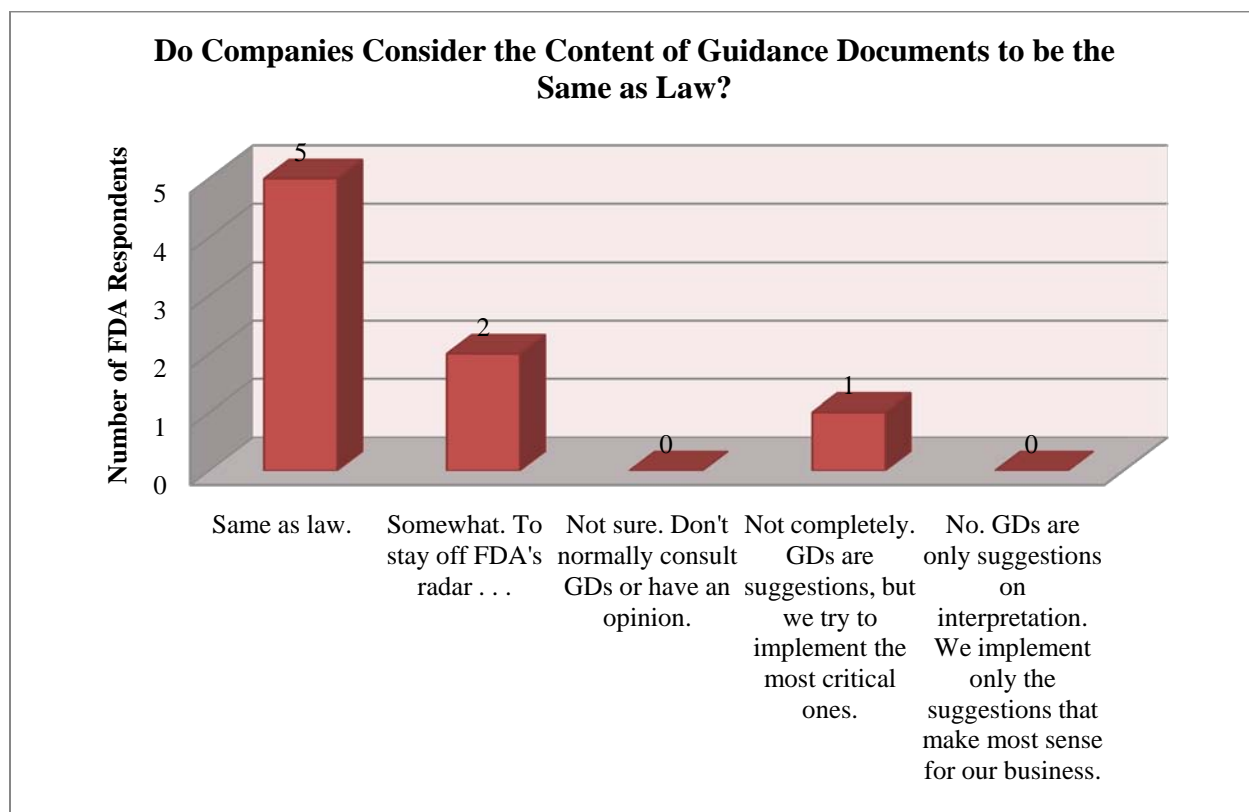


Figure 29 – FDA Respondent Views on Whether Companies Equated Guidance Documents With Laws

When questioned about whether guidance documents closely followed the intended meanings of the regulations, the FDA respondents unanimously agreed that they did follow the intended meanings of the regulations, as indicated in Figure 30. This is similar to the industry responses to the same question.

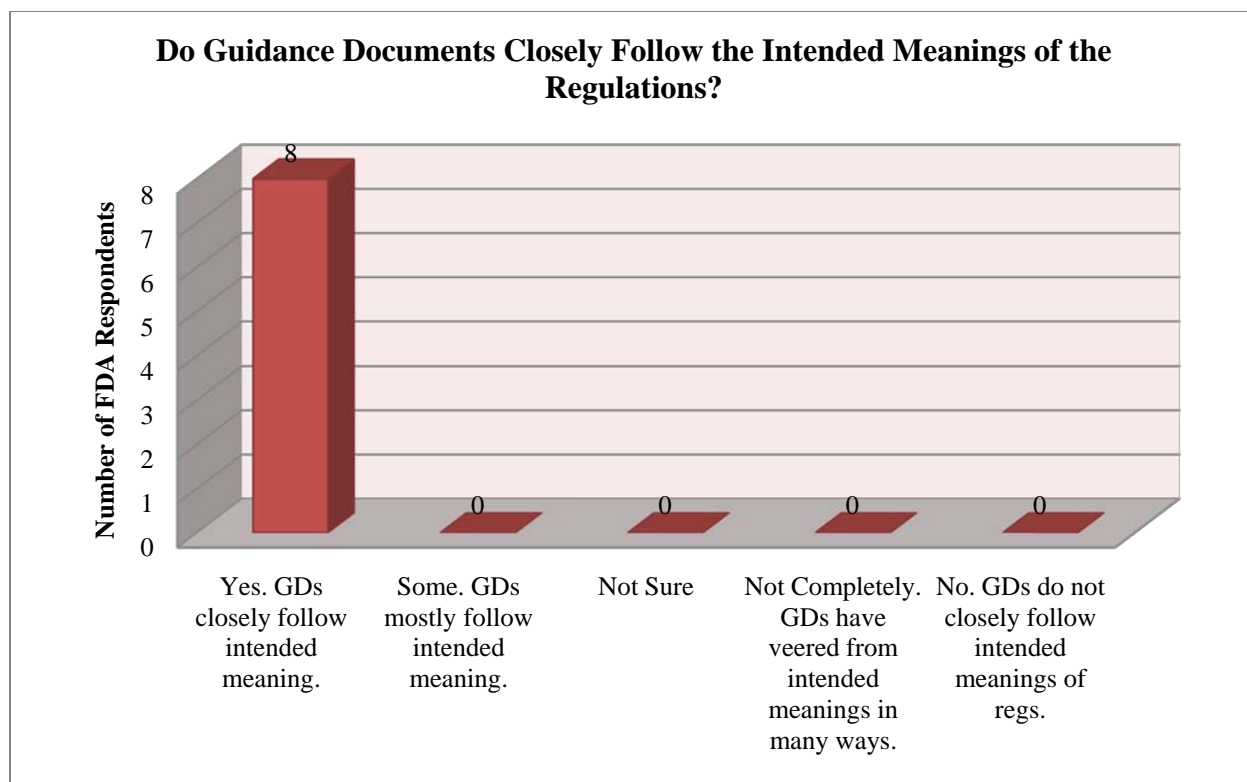


Figure 30 – FDA Respondents Who Felt that Guidance Documents Followed the Intended Meanings of the Laws and Regulations

Also similar to how industry respondents replied, FDA respondents were divided in their opinions on whether guidance documents were a good medium for testing new regulations before implementing them as regulations. One respondent replied “yes”, while a second respondent stated that it would be acceptable as long as the spirit of the regulations was still conveyed by the guidance document. However, whereas the industry responders with a negative response were emphatic and stated without hesitation that this was not an appropriate use of guidance documents, the three FDA negative respondents were less forceful in conveying their opinions. Figure 31 depicts FDA respondents’ thoughts on using guidance documents to test out potential new regulations.

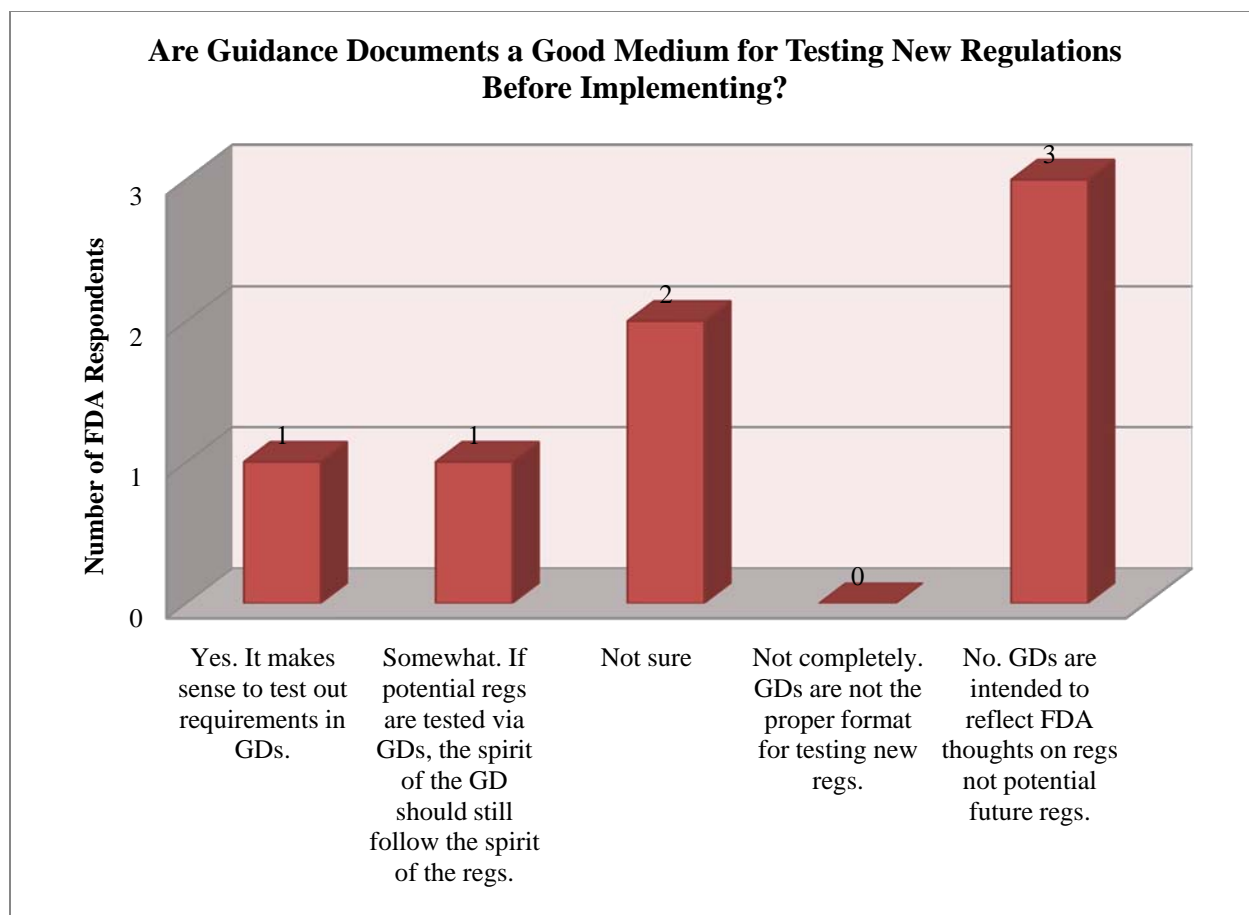


Figure 31 – FDA Respondents on Whether Guidance Documents Are a Good Medium to Test Potential New Regulations

In discussing the impact of guidance documents on the safety and effectiveness of medical products, the FDA respondents had similar responses to their industry counterparts, but they were far more skewed towards guidance documents having a positive impact. While industry respondents replied with a 13 to 5 ratio in favor of guidance documents having a positive impact on safety and effectiveness (Figure 12), the FDA respondents were 7 to 1 in favor of guidance documents having a positive impact, as depicted in Figure 32. Perhaps the most interesting aspect of these responses is that the lone negative response came from the highest ranking FDA respondent, who stated that guidance documents were “not intended to deal with

design and safety” and that it was not the FDA’s responsibility to explain how companies should design products. It was the FDA’s responsibility, he continued, to assess a product’s safety and effectiveness “using sound scientific principles”²⁰. These are valid points, but the reason many may disagree with this senior FDA official is that safety and effectiveness are more than design principles employed in the creation of the product. Safety and effectiveness are also impacted by how that design is transferred to a manufacturing site and how the company has decided to prove the safety and effectiveness of that design via clinical trials. Unlike the pure design aspect, these other aspects are very clearly covered by guidance documents.

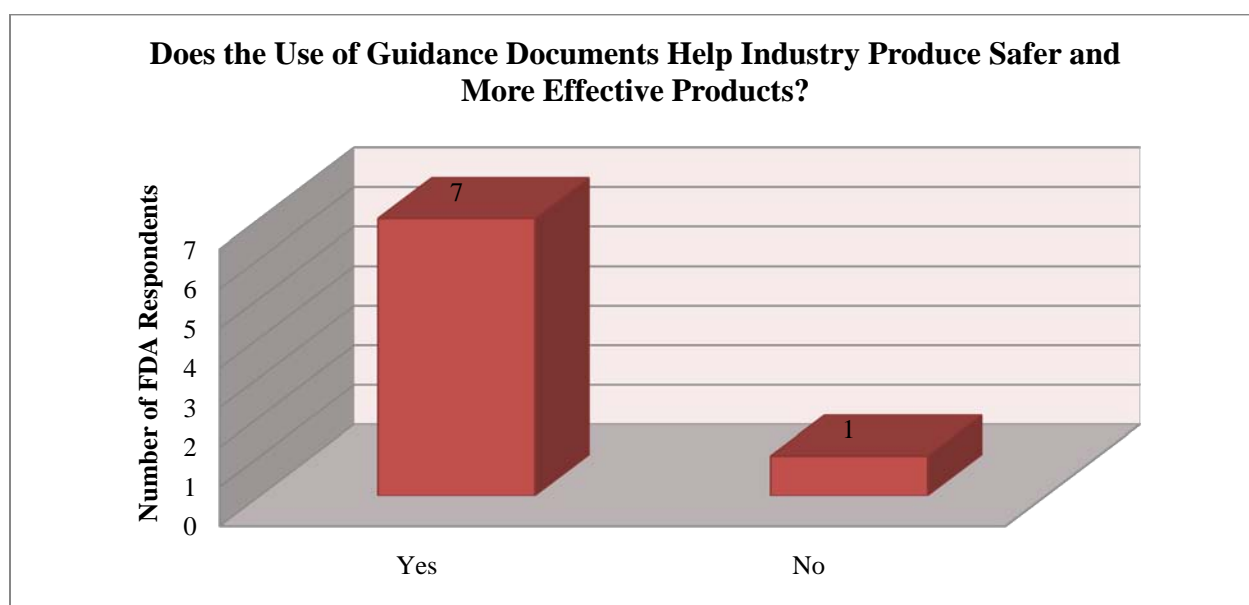


Figure 32 – FDA Respondent Opinions on Whether or Not Guidance Documents Helped Produce Safer and More Effective Products

In comparing the FDA respondent opinions to industry respondents, one of the areas in which agreement between the two groups was strongest was in their opinions that guidance documents were effective tools for helping a company achieve and maintain compliance with the regulations. This is evident when comparing Figure 13 with Figure 33, which depict the opinions

of industry and FDA respondents, respectively, on whether guidance documents were effective compliance tools. In the case of the FDA respondents to this question, all but one respondent answered in the affirmative, although one affirmative respondent had a few issues with guidance documents that impacted his perception of guidance document effectiveness.

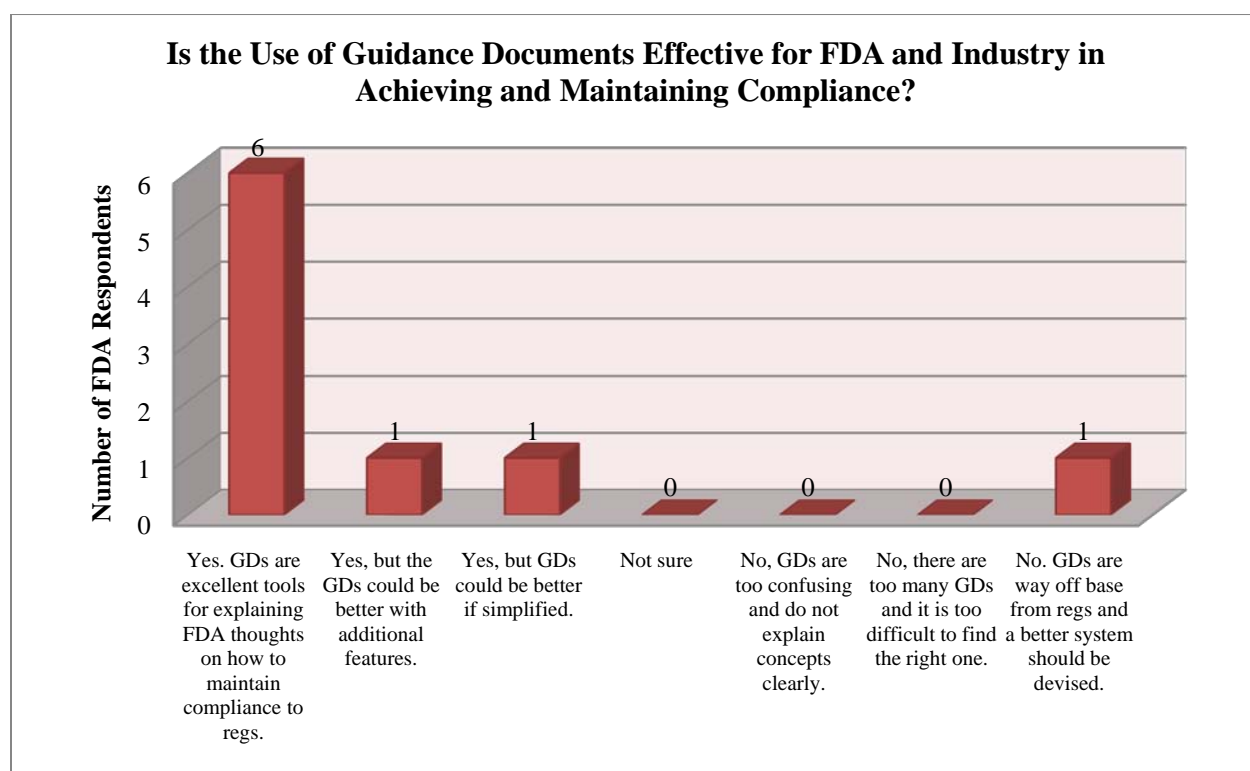


Figure 33 – FDA Respondent Opinions on Effectiveness of Guidance Documents

Potential Negative Impacts of Guidance Document Usage

When discussing possible negative impacts of guidance document usage, industry and FDA respondents both agreed that over-dependence on guidance documents was not a legitimate concern. In both cases, as depicted in Figures 17 and 34, half of the respondents strongly disagreed that this was a concern and only three total individuals from both groups added together agreed with the concern. One consultant stated that even if a company did implement guidance documents without consideration of the corresponding regulations, “they [would] still

be compliant so it's not really an issue;" moreover, if companies were diligent in their hiring practices, they would have competent regulatory personnel who know to use all available information to make regulatory decisions²⁵.

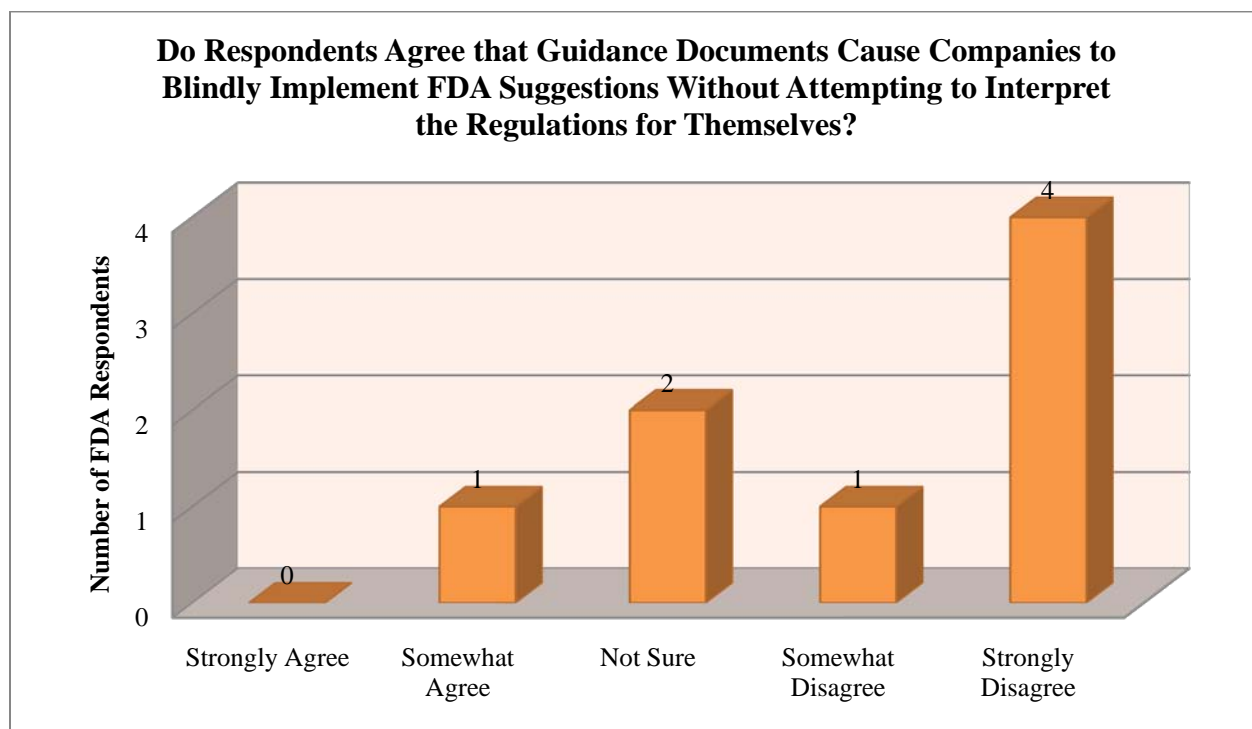


Figure 34 – FDA Respondent Opinions on Whether Guidance Documents Made Companies More Likely to Not Attempt to Understand the Regulations for Themselves

One might expect when speaking with FDA personnel that a case as important as *United States v. Utah Medical Products, Inc.* would be well-remembered and lessons would be shared and learned by all. However, when queried on whether they were aware of an FDA inspector ever citing a company for a nonconformance to a guidance document, as depicted in Figure 35, four of the eight FDA respondents, all of whom were employed by the FDA during the trial, did not recall ever hearing about such an event. Obviously, this raises concerns that such an event could happen again, although it may be less likely with such measures as TurboEIR and the

levels of supervisor oversight currently in place. However, as a philosopher once noted: “Those who cannot remember the past are doomed to repeat it”²². Of note is that the three respondents, who were aware of this type of situation happening but who thought that this type of situation would not happen again, were all field office employees who conducted establishment inspections. So, perhaps this is a case where those who were most directly affected by this type of situation were more likely to remember and learn from past inspection errors.

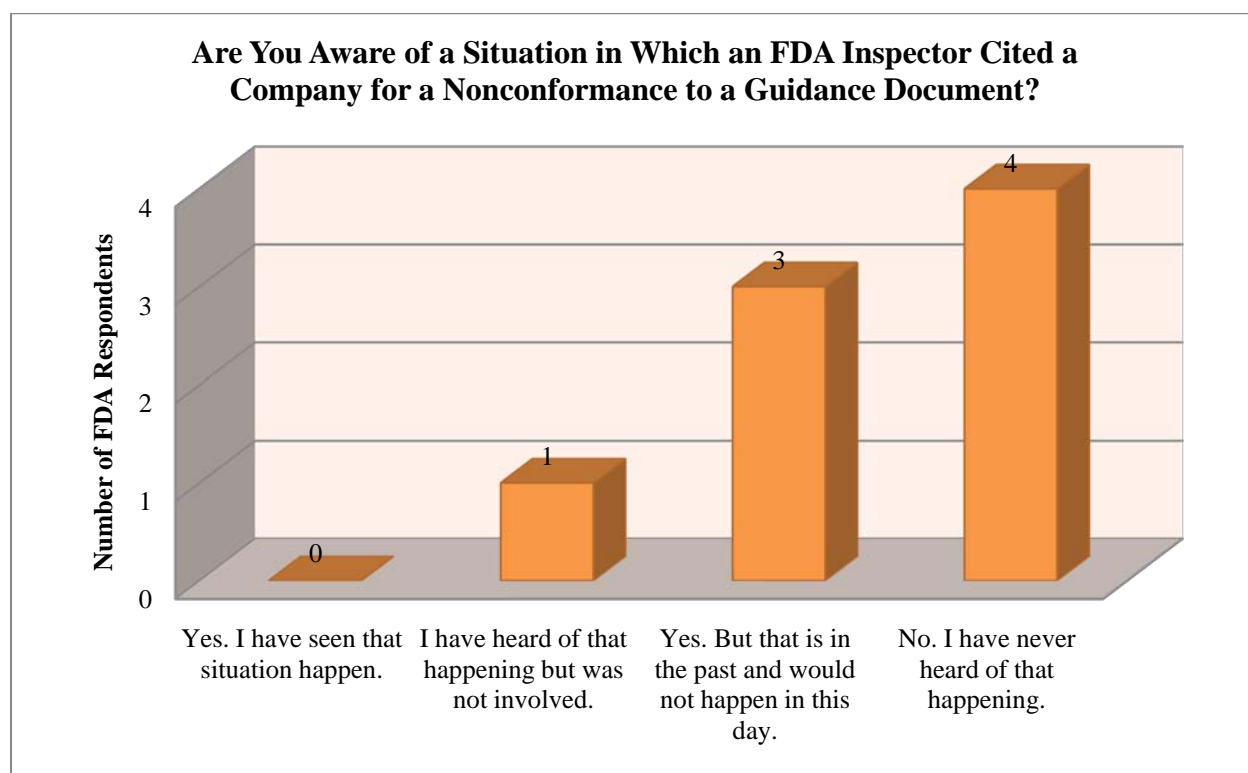


Figure 35 – FDA Respondents Aware of FDA Inspectors Citing Nonconformances to Guidance Documents

When questioned about whether they were aware of product clearances or approvals being held up due to noncompliance with a guidance document, when not specifically covered by the regulations, the FDA respondents gave significantly different answers from the industry respondents. While a majority of industry respondents had heard of this type of situation

occurring, only one of the eight FDA respondents had heard of this occurring. A possible explanation for this discrepancy could be that no one from a product review group was interviewed during this research. It could be a simple explanation of one work group not knowing what goes on in another work group, a common issue in industry as well. Figure 36 depicts FDA respondent answers to questions about new product review practices with regard to guidance documents.

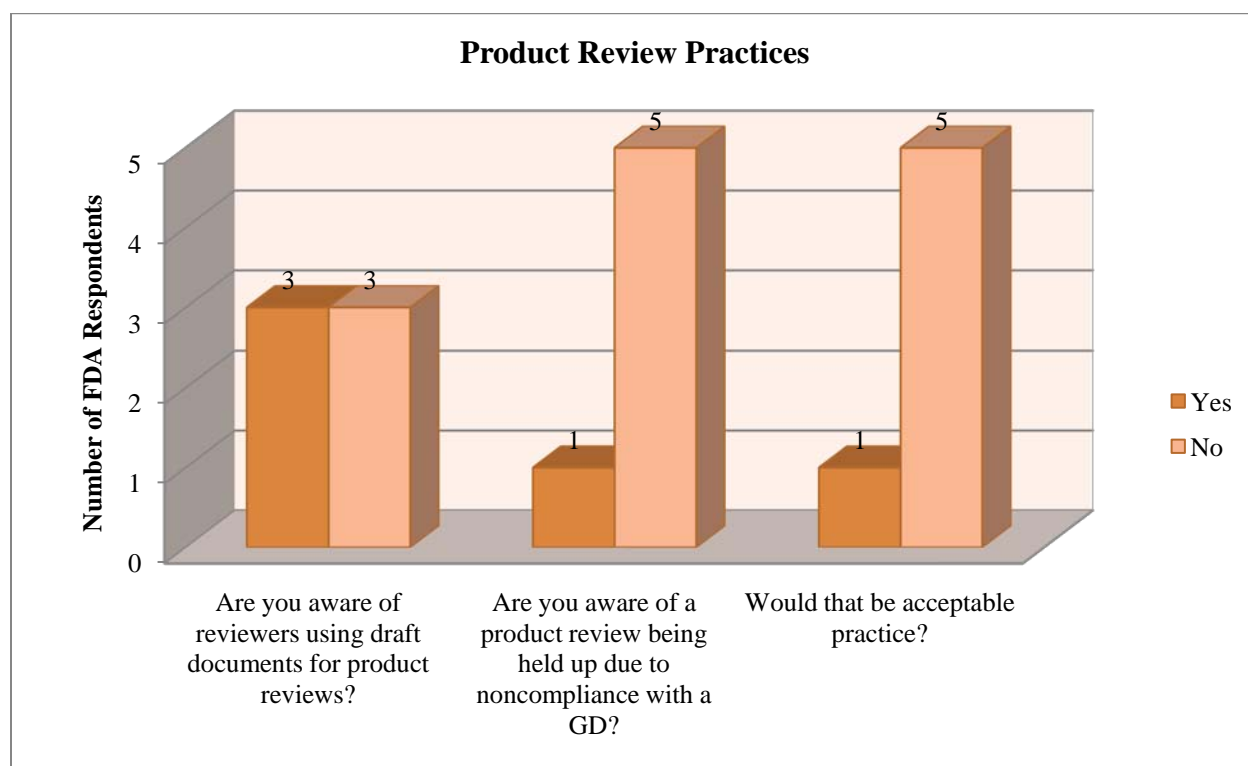


Figure 36 – FDA Respondent Responses to Questions About Guidance Document Usage in Product Reviews

Improving Guidance Documents

A major improvement effort to the guidance document creation and revision process was implemented in the form of the Good Guidance Practices (Title 21 CFR 10.115). These regulations provide the necessary framework for “developing, issuing, and using guidance

documents”¹⁶. These regulations are responsible for defining and classifying guidance documents, establishing the system of reviewing and commenting on draft documents, stating that neither the FDA nor industry is legally bound by the content of guidance documents, etc. When queried about the types of effects Good Guidance Practices (GGPs) have had on the guidance document system, the results were essentially equally divided between a positive effect and a neutral effect, as shown in Figure 37. Note that two individuals answered yes to both positive reasons causing the data to appear skewed to the positive side.

Those who gave positive responses recognized that, under GGPs, guidance documents take significantly longer to implement. However, they also stated that the resulting quality of document is worth the extra time and effort. Those who answered “neutral” recognized the improvement to document quality as a positive attribute, but they were also frustrated about guidance documents taking months or even years to finalize and implement. These individuals felt as though the positive impact to the document quality was effectively cancelled out by the lack of timely implementation.

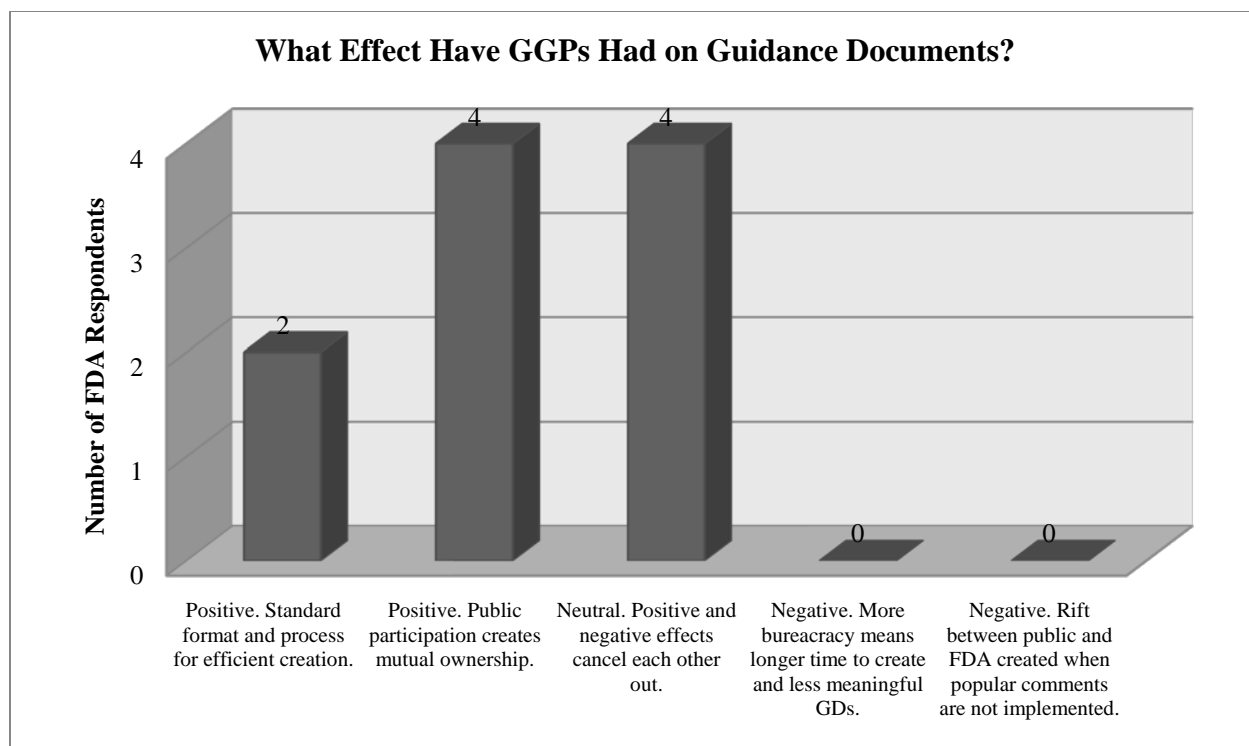


Figure 37 – FDA Respondent Opinions on Effect of GGPs on Guidance Document System

Similar to their industry counterparts, the FDA respondents felt that, overall, the guidance document system was reasonably effective. However, five of the eight FDA respondents stated there was definite room for improvement in the system for creating and revising guidance documents. They felt that guidance documents must be created and implemented much quicker in order to keep up with technological advances. Figure 38 depicts FDA respondent feelings on necessary changes to the guidance document system.

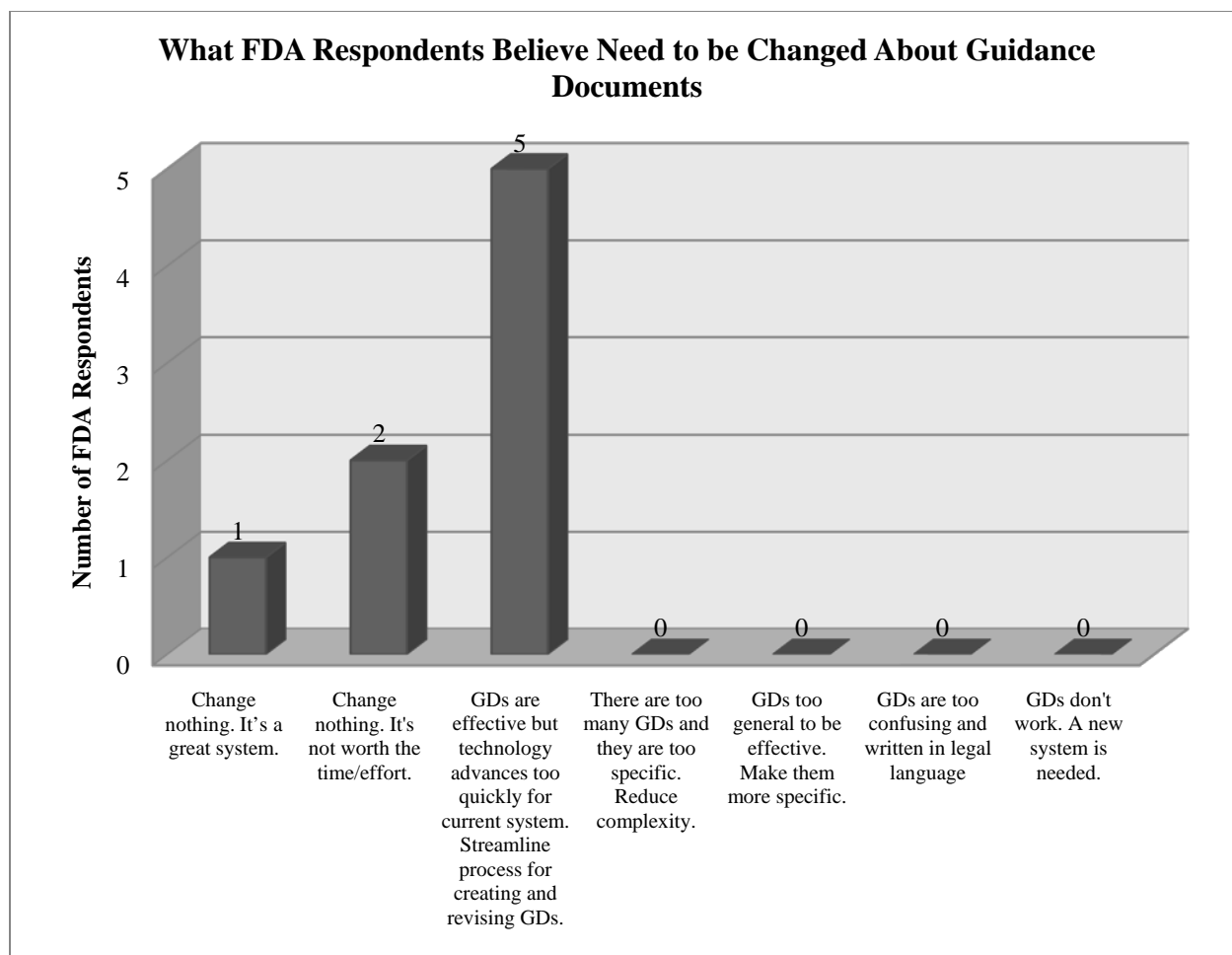


Figure 38 – FDA Respondents on Necessary Changes to the Guidance Document System

As with the industry respondents, when asked about their vision of a new system to take the place of the current guidance document system, one of the respondents mentioned using a Wiki-based program for developing and finalizing guidance documents so that the system would be easier to search and make modifications as needed. Other suggestions were relatively simple in scope, such as making it faster or easier to search.

CHAPTER 5

ANALYSIS AND CONCLUSIONS

Analysis

In comparing the results of medical product industry respondents to FDA respondents, several areas were nearly identical between the groups. One area was the determination of guidance document usage in the past, present and future. Industry responses (Figures 4, 5, and 6) nearly match exactly with their FDA counterpart responses (Figures 24, 25, and 26). This indicates that the FDA and industry respondents were reasonably close in their opinions of how guidance documents were utilized. This is important because, ideally, the FDA should understand the needs of industry so that they can supply guidance documents to meet those needs. One could surmise that, in general, the FDA does a good job with this since the respondents were in such strong agreement.

Unsurprisingly, another area in which the FDA and industry matched well was in how much their management groups encouraged the use of guidance documents with their employees. It was expected that FDA respondents (Figure 27) would be unanimous in stating that management supported the use of guidance documents since guidance document usage was a requirement of the GGP, and, indeed, this was the case. Similar to the FDA respondents, the industry respondents (Figure 7) were nearly unanimous in claims of management support of guidance document usage.

Both groups of respondents (Figures 8 and 28) also agreed in thinking that guidance documents were useful for understanding the FDA's current thinking on regulatory matters. Since this is essentially the purpose of a guidance document, this is reasonable.

The first area in which the two groups diverged noticeably in their opinions was when queried on whether medical products companies viewed guidance documents to be equivalent to regulations or laws. The FDA respondents (Figure 29) nearly all stated that industry personnel viewed guidance documents the same as law or very nearly the same as law. Alternatively, industry respondents (Figure 9) were nearly split equally in their opinions. This was a significant divergence since it indicated that the FDA respondents placed guidance document content at a higher level of importance than many industry respondents.

The two groups of respondents were reasonably close once again when providing opinions on whether or not guidance documents followed the intended meanings of the regulations. The FDA respondents (Figure 30) unanimously opined that guidance documents closely followed the intended meaning of the regulations. The industry respondents (Figure 10) were nearly unanimous in stating that guidance documents either closely followed or mostly followed the intended meaning of the regulations. Perhaps this is a positive outcome of the GGPs. Since industry has a chance to comment and assist in the creation of guidance documents, they assist the FDA in keeping expectations realistic and within the scope of the intended meaning of the regulations.

If the responses of the two FDA participants who shared no opinion about whether guidance documents were a good medium for testing new regulations were removed, the charts of these two groups would look very similar. Both groups were reasonably split between

responses on the positive and negative ends of the spectrum. This was an unexpected result. One might think that industry respondents (Figure 11) would be skewed to the negative side, since additional guidance requirements could mean additional cost or additional time to market. Alternatively, it could be hypothesized that FDA respondents (Figure 31) would be skewed to the positive side due to frustrations with the long and inefficient rulemaking process by which new regulations are created. However, this was not the case.

In determining the ultimate impact of guidance documents on medical products, safety and effectiveness are key. Both groups had similar responses to this query, but the industry respondents (Figure 12) had a slightly smaller positive skew than FDA respondents (Figure 32). These responses were very interesting. Many of the negative responses focused on the impact of guidance documents on compliance without considering the impact of regulatory compliance on safety or effectiveness. A few expounded by stating that safety and effectiveness were purely a function of design, and it was not the FDA's responsibility to tell medical products companies how to design their products. However, safety and effectiveness go beyond product design. They are also heavily impacted in how those designs are transferred into a manufacturing process and how a company chooses to prove the product's safety and effectiveness.

From a compliance standpoint, FDA (Figure 33) and industry respondents (Figure 13) were both nearly unanimous in stating that guidance documents were effective tools for helping a company achieve and maintain compliance with regulations. This was expected because it is a system that has been in place for many years and has been generally accepted by industry. Although many respondents from both sides commented about the contents of a particular guidance document, nearly all agreed that guidance documents were an effective regulatory tool.

When asked about the frequency of contacting the FDA and regulatory consultants for guidance document clarifications, industry respondents (Figure 14) stated they contact consultants slightly more often than they contact the FDA. One industry respondent commented that it is not always necessary to confirm with the FDA or consultants except that it makes his superiors feel more confident in his regulatory decisions²³. Also of significance was that of those seven industry respondents who had utilized guidance documents produced from multiple FDA centers (Figure 16), four of them stated that CDRH guidance documents were the best of all centers in terms of both the content and the availability of relevant documents.

A reasonable concern with using guidance documents is that companies may implement changes to their quality system based on the contents of guidance documents without attempting to understand the regulations for themselves. This could result in a quality system that is not adequate for the specific needs of the company. When queried about whether this might be a legitimate concern, a majority from both sets of respondents (Figures 17 and 34) stated that they either somewhat disagreed or strongly disagreed that this was a concern. One medical device industry consultant stated that, even if that was the case and someone went strictly by the guidance documents, their quality system would still be compliant²¹.

Not only was there a concern that industry personnel could become overly dependent on guidance documents, there was also a concern that FDA personnel may become too dependent on guidance documents as well. This concern may be heightened with FDA personnel since they do not deviate from guidance documents except in extreme cases and only with supervisory approval¹⁸. Five of the eighteen industry respondents (Figure 18) indicated they were aware of a situation in which an FDA inspector had cited a company for nonconformance to a guidance document. Four of the eight FDA respondents (Figure 35) had also heard of that type of situation

occurring, although three of them were of the opinion that this type of event would not likely happen again due to the current controls in place, such as TurboEIR and the amount of supervisory oversight of field activities. In addition, twelve industry respondents (Figure 19) indicated they were aware of new product approvals or clearances being held up due to noncompliance with guidance documents, whereas only one FDA respondent (Figure 36) was aware of this type of situation.

The Good Guidance Practices (GGPs) have had a significant effect on the creation and revision of guidance documents. When asked their opinions on the overall impact to the guidance document system, the FDA respondents (Figure 37) were split evenly between GGPs having a positive impact on the guidance document system and GGPs having a neutral impact because the positive and negative impacts effectively cancel each other out. As previously discussed, the major concern with GGPs was the impact to how long it takes to implement new or revised documents.

One of the most significant effects created by the GGPs was the review and comment process for developing or revising a guidance document. Eleven of the eighteen industry respondents (Figure 20) had commented on draft guidance documents at some point in their careers. However, only eight of those eleven industry respondents felt as though the FDA gave serious consideration to their comments. Alternatively, the FDA respondents were unanimous in their belief that the FDA takes comments seriously.

In the spirit of continuous improvement, both sets of respondents (Figures 21 and 38) were questioned to determine what needs to be changed about guidance documents and the guidance document process. In both groups, the majority of respondents commented that,

although guidance documents were effective, when compared to the speed of technological advances in the medical products industry, the pace of creating and revising guidance documents was much too slow. The process should be streamlined and sped up in order to have the necessary documents in place to guide new product submissions for newer technology products.

Conclusions

The guidance document system has been in place for several years and many in the medical products industry agreed that the quality of guidance documents has improved with the implementation of the Good Guidance Practices. For the most part, assuming that the industry respondents of this research are representative of the industry as a whole, medical products industry management encourages the use of guidance documents by its employees because they feel that guidance documents are useful in understanding the FDA's current thinking on regulatory issues and that guidance documents closely follow the intended meanings of the regulations. Industry opinions are reasonably split with regard to how strictly they follow guidance documents. One segment treats guidance documents essentially as if they were laws; the other chooses to view them more as suggestions or recommendations to be considered on a case-by-case basis depending on what is best for the business.

Guidance documents are generally viewed as having a positive impact on the safety and effectiveness on medical products. In addition, a large percentage of industry representatives view guidance documents as being effective at helping industry and the FDA achieve and maintain compliance with the regulations. Although most industry respondents disagreed with the notion that medical products industry personnel may become too dependent on documents which may cause them to implement FDA recommendations without taking the time to learn and understand the regulations for themselves, many of them claimed that they were aware of

situations in which the FDA has cited a company for nonconformance to a guidance document or in which an FDA reviewer has delayed a product approval or clearance due to nonconformance with a guidance document, indicating a potential over-dependence on guidance documents by FDA personnel.

With a few exceptions, assuming that the FDA respondents of this research project share the opinions and thoughts of a typical FDA employee, FDA employees generally agree with the medical products industry on most thoughts with regard to guidance documents. In addition, FDA employees were split in their opinions on the impact that GGP's have had on guidance documents. One group felt strongly that they have had a positive impact based on the quality of new documents; the other felt that the positive and negative impacts canceled each other out resulting in a neutral impact on guidance documents. The negative impact most often mentioned was the time it took to create or revise a guidance document due to the many steps in the process and the many levels of bureaucracy through which the document must move. In fact, one industry respondent mentioned a specific guidance document that was currently over two years old and still in draft status²⁴.

Moving Forward

Very few suggestions were made by respondents on how to improve the guidance documents themselves. One can conclude that most FDA and medical products industry respondents were pleased with the format and content of guidance documents, with the exception of some documents being out of date and needing revisions based on newer technologies. Alternatively, many suggestions to improve the guidance document creation and revision process were made by both groups of respondents.

The most intriguing suggestion to improve the guidance document creation and revision process was made by three respondents, including members of both groups. It involved effectively scrapping the current system and implementing a web-based Wiki system in which industry, FDA, consumer protection groups, and other interested parties could join together to submit comments and modifications through an internet portal. The advantage of a Wiki system is its openness. Anyone can see the comments, edits and other modifications simply by going to the website. In addition, there is accountability in that anyone can see who made which edits. In this type of arrangement, there would obviously be an administrator in the FDA for the document, probably one who leads or represents a committee overseeing the guidance document in question. This committee or person would be responsible to review the edits and comments and make decisions on what is appropriate for the final document, not months later after all comments had been received but within a few days of the comment while it is fresh and relevant.

It is difficult to quantify the impact this type of system might have on the guidance document creation or revision process. Essentially it combines the creation process with the review and comment process so that participants who would normally just comment on a completed draft could have more of a say in what is actually being written as it is written. This is likely to result in a very significant reduction in the time required to create or revise a guidance document.

Some points to consider when reviewing this research are the limitations in the number and types of respondents. FDA respondents were limited to current and former FDA employees located at FDA headquarters in Rockville, MD and the Atlanta field office. No FDA employees from other field offices or other locations chose to participate. Also, industry respondents were limited to US-based employees. This decision was based on potential time-zone differences,

language differences, and other factors that could affect the outcomes of the phone interviews with international participants. Another limitation is that very few of the industry respondents were from small manufacturing companies. In addition, a large portion of the respondents were from medical device backgrounds. Finally, the overall sample size was smaller than desired, especially the FDA respondents.

In order to improve this research project, additional efforts need to be made to diversify the respondent pools. This should allow the researcher to gain a broader spectrum of responses and should increase the researcher's confidence that the results are representative of the entire medical products industry and the entire FDA organization. To diversify the FDA respondents, the researcher should attempt to obtain respondents from each of the medical product centers of the FDA: CDRH, CDER, CBER, and CVM. In addition, the researcher should attempt to obtain respondents from field offices in each of the FDA's US regions.

When attempting to diversify the industry respondent pool, the researcher should obtain respondents from worldwide locations who sell medical products in the US, and are, therefore, familiar with the applicable FDA regulations and guidance documents. The researcher should also obtain a more diverse mix of expertise in product types and a more diverse mix of company types and sizes.

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