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February 27, 2012

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

Lisa M. Dwyer, Office of Policy
Office of the Commissioner
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 32, rm. 4228
Silver Spring, MD 20993

Re: Docket No. FDA–2009–N–0247; Comments on the Food and Drug Administration Transparency Initiative: Food and Drug Administration Report on Good Guidance Practices: Improving Efficiency and Transparency

Dear Ms. Dwyer:

As we have said previously in this docket, the Combination Products Coalition ("CPC") commends the U.S. Food and Drug Administration ("FDA" or "Agency") for its efforts to increase transparency with regard to Agency regulation and enforcement. As an organization focused on advancing combination product policy, the CPC wholeheartedly supports transparency throughout the Agency and specifically in the area of combination product compliance and enforcement.

But there is a problem. There are three areas related to combination product transparency that often get neglected due to competing priorities:

1. The production of guidance documents to address combination product questions;
2. The release of information about combination products; and
3. FDA response to industry comments and other input the Agency receives on guidance.

We recognize those are broad, sweeping statements, and as such they are not universally true. There are notable exceptions. But unfortunately there is also general truth to those statements. In this letter we will review the evidence that supports each of those statements and, more importantly, make several positive suggestions for how the situation can be improved.

By way of background, the CPC is a group of leading drug, biological product, and medical device manufacturers with substantial experience and interest in the combination products arena. One of the principal goals of our organization is to work collaboratively with the Agency on issues affecting combination products, in order to advance our common missions of providing the best possible health care for patients. Because of our diverse, cross-industry membership, we think the CPC brings a broad and unique perspective to issues affecting combination products and the Agency's transparency.

To develop this comment, we consulted the large trade associations in the drug, device and biological products areas for ideas on possible solutions. We also reached out to some known industry thought leaders, as well as leading attorneys in the food & drug law bar. We did this in an effort to make these proposed solutions as sensible and well-crafted as possible. We believe that many of the ideas in this letter have wide support.

Executive Summary

In this comment letter, we request enhancements related to openness and transparency during guidance development in three broad areas:

1. Improving transparency with regard to combination products by:
    a. Streamlining the internal FDA process for developing combination product guidance and rules (which currently requires sign-off by all three implicated Centers plus several other offices);
    b. Producing more guidance on combination products, addressing priority areas such as:
        i. When submissions are required for product modifications,
        ii. When multiple submissions are required, and
        iii. The jurisdictional guidance provided in the inter-Center agreements; and
2. Ensuring that more Agency records with regard to combination product regulation are released to the Agency's website, such as:
    a. The Agency's responses to requests for designation,
    b. Form FDA-483s issued to establishments manufacturing combination products, and
    c. New drug approvals.
3. Enhancing public participating and collaboration in the guidance development process by:

a. Improving the process by which proposed guidance documents may be submitted so as to ensure they can be tracked and ultimately responded to by the Agency;

b. Imposing on itself a requirement that the Agency respond to the comments made during the course of guidance development; and

c. Clarifying through the publication of a new guidance document, a draft of which we are submitting, that the Agency and industry may indeed communicate and collaborate during guidance development.

We believe that many of these objectives may well simply have fallen by the wayside as a result of the extraordinarily tight budgets, limited manpower available at the Agency, and competing priorities. While the pressure to make do with fewer resources is certainly understandable, meaningful response to public input is simply too important to be shut off.

General Comments on FDA Report

We offer these comments on the *FDA Report on Good Guidance Practices: Improving Efficiency and Transparency* as issued in December 2011. We are not going to comment section by section, but rather more holistically.

At a high level, we are concerned that the report puts emphasis in the wrong place. FDA's report focuses mostly on how to save money by making the internal processes of developing guidance more efficient. We certainly support that effort and the principles articulated in the report, but the Agency's effort stops way too short of the President's goal. The President clearly directed federal agencies to examine their guidance processes to ensure an appropriate level of public involvement and collaboration,[1] and there is much too little regarding those topics in the report.

We do applaud the Agency for including on pages 16–18 discussion about using techniques such as webinars and social media to increase awareness regarding draft—not just final—guidances. Certainly creating awareness of proposed guidance documents is a worthy objective. These tools also offer some, albeit limited, opportunity for dialogue. Large webinars with hundreds of people and social media are not designed to create an in-depth dialogue, but mostly for awareness. We also appreciate that on page 5 the report notes that the public can submit guidance documents, but we will talk more about that below.

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[1] Exec. Order No. 13,563, 76 Fed. Reg. 3821 (Jan. 21, 2011), *available at* http://www.gpo.gov/fdsys/pkg/FR-2011-01-21/pdf/2011-1385.pdf. The general principle established in this presidential order is described as the following:

> Our regulatory system must protect public health, welfare, safety, and our environment while promoting economic growth, innovation, competitiveness, and job creation. It must be based on the best available science. ***It must allow for public participation and an open exchange of ideas.*** It must promote predictability and reduce uncertainty. It must identify and use the best, most innovative, and least burdensome tools for achieving regulatory ends. It must take into account benefits and costs, both quantitative and qualitative. It must ensure that regulations are accessible, consistent, written in plain language, and easy to understand. It must measure, and seek to improve, the actual results of regulatory requirements.

Id. (emphasis added).

But the vast majority of the report is focused on streamlining internal decision-making and operations. We think that's interesting, revealing, and frankly troublesome. It's troublesome because right now the Agency is not appropriately utilizing public participation in the guidance development process. Actually doing something with public input is just as important, if not more important, than going to great lengths to solicit it. So the majority of this comment letter will focus on ways that the Agency can improve its ***utilization*** of public input, not just its ***collection*** of public input.

Beyond our concerns with the guidance development process generally, we also believe that FDA has missed an opportunity to strengthen the internal process for developing combination product guidance specifically. Combination product guidance is unique because of its cross-Center ownership. As the Agency maps out more efficient processes for initiating and developing guidance documents, the report completely omits any discussion of how that's done in the combination products setting where multiple stakeholders are involved. We think that omission needs to be addressed.

With that, we will turn to our two primary points in this comment letter: (1) the need for more combination product guidance and (2) the need to utilize public input better.

Guidance Development and Rulemaking for Combination Products

Among FDA regulated articles, combination products are unique in that, by definition, they are combinations of separately regulated drugs, medical devices, and biological products. Unfortunately, within the FDA's management structure, that puts them in no man's land. In a sense, they belong to everyone and also belong to no one. Unfortunately, that is the worst of all worlds, especially in this environment where user fee agreements drive Agency priorities.

By belonging to everyone, for the FDA to articulate policy with respect to combination products, the Agency must generally get people in the three different affected Centers, the Office of Combination Products, and others (like the Chief Counsel's Office) to agree. That simply multiplies the work required and the logistical challenges involved. Given the scarce resources, the result is very little guidance being produced for combination products.

By belonging to no one, at least in the sense that no one has complete ownership of combination product rules, responsibility is lost and combination products get neglected. Examples of that abound:

1. Each of the three responsible Centers publish guidance on a regular basis that addresses the issues unique to the articles they regulate, but without any written consideration of how those rules might be applied in the case of a combination product. Frankly, nearly every time a Center puts out guidance, the Center ought to think about whether the guidance potentially creates any unique issues for combination products and address those issues in the guidance.

2. Even outside the Centers, when officials in the Office of the Commissioner act, they often ignore combination products. For example,

a. In our comment from last December to this very transparency docket,[2] we noted that the drive to put enforcement related data on the Agency's website neglected making combination product status a searchable field.

b. Earlier this year when FDA revamped its website, combination products were all but removed. It is now very difficult for the public to even find the relevant pages that describe combination product requirements in the new website.

c. In its January 2011 Transparency Report, the Task Force describes how inquiries regarding the regulatory process applicable to specific product areas will be handled; however, combination products are not addressed.[3] To take a more specific example, Action 4 creates email addresses to which industry can send questions regarding the regulatory process applicable to specific product areas, but here again combination products are omitted.[4]

d. The FDA Basics webpage created under the Transparency Initiative lists several product areas—foods, cosmetics, dietary supplements, medical devices, radiological, animal veterinary, drugs, tobacco, and biologics—under Main Topics, yet does not mention combination products. Indeed, a search of "combination product" in the FDA Basics search box provides only one result, a link to a basic question about what products are not considered tobacco products.[5]

This information should be provided for combination products just as it is provided for other types of regulated articles. Indeed, having this information is particularly important in the combination product area, where many policies remain in flux. Practical evidence of enforcement, application of key regulations, and other information would greatly clarify Agency expectations for combination product manufacturers.

By belonging to everyone, even with the able assistance of the Office of Combination Products, the Agency has been utterly unable to collectively produce rules and guidance in several areas key to the development of combination products. Those areas of policy gaps include:

- Good Manufacturing Practices ("GMPs") for Combination Products – The Agency announced its intent to publish rules on combination product GMPs in early 2006. Over three years later, in September 23, 2009, proposed rules were published. Most

[2] December 1, 2011 Comment letter from the Combination Products Coalition to Docket Number FDA-2009-N-0247; FDA Transparency Initiative: Proposals For Public Comment To Increase Transparency By Promoting Greater Access To The Agency's Compliance And Enforcement Data.

[3] *See* FOOD & DRUG ADMIN., U.S. DEP'T OF HEALTH & HUMAN SERVS., FDA TRANSPARENCY INITIATIVE: IMPROVING TRANSPARENCY TO REGULATED INDUSTRY 11–17 (Jan. 2011), *available at* http://www.fda.gov/downloads/AboutFDA/Transparency/TransparencytoRegulatedIndustry/PhaseIIITransparencyReport/UCM239088.pdf.

[4] *Id.* at 17. The product areas include: foods, cosmetics, dietary supplements, medical devices, radiological, animal veterinary, drugs, tobacco, and biologics. *Id.*

[5] U.S. Food & Drug Admin., Search Results: "Combination Product", http://google2.fda.gov/search?q=%22Combination+product%22&client=FDAgov&proxystylesheet=FDAgov&output=xml_no_dtd&sort=date%253AD%253AL%253Ad1&site=FDAgov-Basics-AboutFDA&x=12&y=11 (last visited Feb. 15, 2012).

recently, we have heard that the Agency hopes to publish the final rules by May 2012. Waiting for information on the application of GMPs to combination products continues to put a strain on manufacturers that need to move forward with new technologies to improve patient care. The wait also leaves critical regulatory issues in a state of ambiguity and flux. The Agency has been reluctant to engage in dialogue on how to apply current requirements for combination product GMPs while the final rules are under development, even though legally, such dialogue is permissible as discussed more below.

- Post-Market Safety Reporting – As with GMPs, the Agency published proposed rules on post-market safety reporting October 1, 2009 and last year predicted the rules would be finalized by the end of 2011. Informally, we understand that the Agency has encountered IT issues that have slowed the Agency's progress with publishing the final rules. As with the development of the GMP rules, industry has also encountered resistance from the Agency with respect to discussing the application of post-market safety reporting requirements to combination products while the rules are under development.

- Implementing Guidance Documents on Combination Product GMPs and Post-Market Safety Reporting – Implementing guidance will be critical to ensure a successful and timely implementation of both of the above-mentioned proposed rules. Stakeholders have commented that publishing these guidance documents, at least in draft form, with the final rules is necessary to ensure stakeholders can comply with the final requirements within the effective date of the rules.

- Reporting Manufacturing and Design Changes to Marketing Applications – The Agency has reported it has been working on a guidance document on this topic since 2006. This is an extremely complex issue that no doubt requires a significant amount of Agency resources, both from OCP and the Centers. It is also a topic on which industry has an acute need for guidance. Due to the CPC's interest in this topic, we developed and submitted a draft guidance document and case studies to OCP with the hope of stimulating Agency thinking.

- Number of Marketing Submissions – The Agency published a Concept Paper on the number of marketing submissions required for a combination product in 2005. The Agency has not produced a guidance document or responses to the comments raised in the industry comments. A docket was not established for this issue, so the public is unable to access any comments submitted.

- Classification issues – In the recent draft guidance, *Classification of Products as Drugs and Devices and Additional Product Classification Issues*, FDA again called into question the validity of the inter-Center agreements. Manufacturers must be able to understand what parts of the agreements remain viable and what parts have been overcome by scientific developments. We must be able to understand, from a very early stage in the development process, whether a product is likely to be considered a drug, device, or biological product. We are particularly interested in any

modifications to the CDRH-CBER agreements, as Agency presentations (as recently as three years ago) indicated that the vast majority of determinations in that agreement were still current.

- Clinical Study Requirements – Clinical trial requirements for combination products were another very highly ranked priority in our industry survey on guidance document needs. These clinical trial issues may include such topics as bioequivalence studies for auto-injectors, human factors as part of Phase III studies, study size required to demonstrate device effectiveness, clinical trial designs for combination products, and number of clinical studies required for medical devices. The Agency has not issued guidance on these issues since the high level guidance on *Early Development Considerations for Innovative Combination Products* in September 2006. The CPC developed and, in February 2009, submitted to the Agency *Draft Guidance for Industry and FDA Staff: FAQs on Pre-Clinical and Clinical Research on Combination Products.*

- Auto-injector Guidance – The Agency issued a draft guidance on *Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products* in April 2009. The CPC submitted comments on this guidance, along with other organizations and manufacturers. Since the comment period has closed, the OCP has explained in public forums that they are working on a second, companion auto-injector guidance that should clarify the numerous ambiguities in the draft guidance that was published almost three years ago. Many members of the CPC—and we would presume other industry stakeholders—are anxious to obtain clarification on the issues raised by the first guidance and with respect to auto-injector issues generally.

To give patients access to safe, effective, and innovative products, manufacturers need transparency, clarity, and regulatory predictability on these important policy development issues. Frankly, the only way to really achieve those objectives is to increase the meaningful dialogue between the Agency and its stakeholders.

We think the President of the United States, Barack Obama, said it well in his memo to Agency heads:

> My Administration is committed to creating an unprecedented level of openness in Government. We will work together to ensure the public trust and establish a system of transparency, public participation, and collaboration. Openness will strengthen our democracy and promote efficiency and effectiveness in Government.
>
> *Government should be transparent*. Transparency promotes accountability and provides information for citizens about what their Government is doing. Information maintained by the Federal Government is a national asset. My Administration will take appropriate action, consistent with law and policy, to disclose

> information rapidly in forms that the public can readily find and use. Executive departments and agencies should harness new technologies to put information about their operations and decisions online and readily available to the public. Executive departments and agencies should also solicit public feedback to identify information of greatest use to the public.[6]

With regard to the goal of transparency, unfortunately FDA simply has a blind spot when it comes to combination products. Because of the structural challenges involved in managing the regulatory oversight of products that by definition span multiple Centers, FDA has neglected combination products in its efforts to be transparent. This is true both for ensuring appropriate guidance and for the release of basic information of value to the industry. FDA needs to bring combination products into greater focus as the Agency works to be transparent.

Proposed Solution

On the one hand, the solution is relatively simple to state. FDA needs to complete the development of the rules and guidance for combination products that we have outlined above. To help the Agency in its prioritization, in our list we have written the items according to our priorities as a representative of the industry. We full well recognize that our priorities are not controlling and that the Agency needs to have its own priorities, but we thought the Agency might appreciate at least hearing how we would rank them.

On the other hand, addressing all of those issues is treating the symptom, and the Agency will probably want to get to the root cause. From the outside, of course, we cannot appropriately propose specific internal changes that would make combination product policy flow more smoothly, but instead we request the Agency convene an internal dialogue as a part of the transparency initiative to discuss what can be done.

We suspect, but do not know, that developing combination product policy is extraordinarily labor-intensive and requires an enormous number of signatures. We also suspect that many of the signatures are required from people who would not prioritize combination product policy highly. We would guess that if the Transparency Task Force examined the process by which combination product policy is developed, the group could identify numerous opportunities for improvement and greater efficiency.

Releasing Information about Combination Products

Compounding the lack of guidance is the lack of basic information regarding the decisions the Agency is making with regard to combination products. As already noted, the CPC has been requesting for years that FDA put on its website compliance information such as Form FDA-483s for facilities that produce combination products. But making matters worse, standard

[6] Transparency and Open Government: Memorandum for the Heads of Executive Departments and Agencies, 74 Fed. Reg. 4685, 4685 (Jan. 26, 2009), *available at* http://www.gpo.gov/fdsys/pkg/FR-2009-01-26/pdf/E9-1777.pdf.

regulatory information that the industry used to obtain from the Agency's website is no longer available.

For example, through its website, the OCP used to share some information with regard to the request for designation ("RFD") process and jurisdictional decisions.[7] However, the OCP has not posted recent decision letters; the most recent letter is dated January 17, 2007.[8] We have found jurisdictional information to be extremely helpful in understanding jurisdiction and classification issues and what FDA Center is the "lead" for a particular product. Other Agency sectors post this information regularly.[9]

Proposed Solution

FDA needs to **e**nsure the public release of data that shows how combination products have been regulated in the past, including:

1. The Agency responses to requests for designation that the Agency had been posting on its website through early 2007, but stopped.

2. For all of the other information that the Agency routinely posts to its website, including enforcement information and approval information, the Agency should include as a search term the opportunity to sort the results according to whether or not a regulated article is part of a combination product. The categories of data would include, but not be limited to:

    a. NDAs

    b. BLAs

    c. Form FDA-483s

    d. Recalls

    e. Adverse events

[7] *See* U.S. Food & Drug Admin., *Combination Products: RFD Jurisdictional Decisions*, http://www.fda.gov/CombinationProducts/JurisdictionalInformation/RFDJurisdictionalDecisions/default.htm (last visited Feb. 15, 2012).

[8] U.S. Food & Drug Admin., *Combination Products: Redacted Decision Letters*, http://www.fda.gov/CombinationProducts/JurisdictionalInformation/RFDJurisdictionalDecisions/RedactedDecisionLetters/default.htm (last visited Feb. 15, 2012).

[9] *See, e.g.*, U.S. Food & Drug Admin., *Vaccines, Blood & Biologics: Tissue Reference Group*, http://www.fda.gov/BiologicsBloodVaccines/TissueTissueProducts/RegulationofTissues/ucm152857.htm (last visited Feb. 15, 2012).

Listening to Industry during Guidance Development

Openness—the President's ultimate goal—depends on more than just transparency. President Obama, after describing the need for transparency above, continued by expressing two additional goals that also contribute to agency openness:

> *Government should be participatory*. Public engagement enhances the Government's effectiveness and improves the quality of its decisions. Knowledge is widely dispersed in society, and public officials benefit from having access to that dispersed knowledge. Executive departments and agencies should offer Americans increased opportunities to participate in policymaking and to provide their Government with the benefits of their collective expertise and information. Executive departments and agencies should also solicit public input on how we can increase and improve opportunities for public participation in Government.
>
> *Government should be collaborative*. Collaboration actively engages Americans in the work of their Government. Executive departments and agencies should use innovative tools, methods, and systems to cooperate among themselves, across all levels of Government, and with nonprofit organizations, businesses, and individuals in the private sector. Executive departments and agencies should solicit public feedback to assess and improve their level of collaboration and to identify new opportunities for cooperation.[10]

FDA has been focusing on the transparency goal, but has not sought ways to increase public participation and collaboration, and indeed those aspects of the Agency's mission have suffered over the last several years.

Outside of combination products, FDA, for the most part, has used guidance to express what the Agency thinks, or expects, in a given situation. What the Agency has not done well (for frankly any regulated product of late) is use the guidance development process to collect and embrace ideas from outside the Agency. We think this is in large part due to workload and the focus on the user fee commitments. We are afraid that FDA staff simply does not have the time to carefully listen to the public. The result is FDA is becoming very insular, using guidance to convey its intentions and not as a vehicle for collaborative dialogue to truly listening to public/industry input. That is quite counter to the purpose of the guidance development system and the objectives of our President. And unfortunately, FDA's latest recommendations do nothing to change that.

[10] *Id.*

We offer three examples to illustrate our point.

1. <u>Not Acting on Guidance Proposed by Industry</u>

a. <u>Problem</u>

FDA occasionally solicits proposed guidance documents from the public, but to our knowledge, the Agency does not act on those proposals when they receive them. According to *Food and Drug Administration Report on Good Guidance Practices: Improving Efficiency and Transparency*:

> Stakeholders also submit citizen petitions to identify policy issues that the Agency may decide to address by issuing guidance. [Note omitted.] Because of resource constraints, however, FDA is not always able to issue guidance in response to stakeholder suggestions, or to issue guidance as expeditiously as it would like.
>
> Recently, several Centers/Offices have been encouraging stakeholders to submit *draft guidance* to the Center/Office, for consideration, at a variety of different industry events, such as trade association meetings and on the FDA website. [Note omitted.] Submitting *draft guidance*, rather than guidance topics, enables the Center/Office to approach a guidance topic with a better understanding of the issues that interest the stakeholder. This may expedite the guidance development process, particularly if the topic involves novel scientific issues.[11]

This makes sense and would seem to be a good way to leverage the Agency's scarce resources. Unfortunately, though, we think the Agency has been so strapped that they have not made use of the proposals submitted. This, in turn, discourages others from submitting.

To allow the public to submit proposed guidance documents, the Agency has a very specific procedure that says:

> You can submit drafts of proposed guidance documents for FDA to consider. When you do so, you should mark the document "Guidance Document Submission" and submit it to Division of Dockets Management (HFA-305), 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.[12]

We have scoured the FDA docket (even requesting assistance from FDA's Dockets Management) and found 6 proposed submitted guidance documents over the last 10 years.

[11] FOOD & DRUG ADMIN., U.S. DEP'T OF HEALTH & HUMAN SERVS., FOOD AND DRUG ADMINISTRATION REPORT ON GOOD GUIDANCE PRACTICES: IMPROVING EFFICIENCY AND TRANSPARENCY 5 (2011), *available at* http://www.fda.gov/downloads/AboutFDA/Transparency/TransparencyInitiative/UCM285124.pdf.

[12] 21 C.F.R. § 10.115(f)(3).

Unfortunately, though, we have not found any action on any of these proposed submitted guidance documents. The proposed submitted guidances are summarized in Table 1.

Table 1: Guidance Documents Submitted to FDA

Date	Submitter	Guidance Document Submitted	Agency Response
June 17, 2003	Roche Diagnostics, Becton Dickinson & Company and Gen-Probe Incorporated collectively	In Vitro Analytical Tests ("IVATs"); Draft Guidance for Industry and FDA (Docket # FDA-2003-D-0696)[13]	No action taken by the Agency.[14]
Mar. 30, 2004	Orthopedic Surgical Manufacturers Association	Clinical Trial Design for Hip Replacement Systems (Docket # FDA-2003-N-0213)[15]	No Agency response in the docket.
Feb. 27, 2009	Combination Products Coalition	Draft Industry and FDA Staff: FAQs on Pre-Clinical and Clinical Research on Combination Products (Docket # unknown)[16]	No written response. The coalition has been seeking to open a dialogue with the Agency on the topic.
Sept. 4, 2009	BQSI Committee	Quality Management System for BioAnalysis Supporting Clinical Trials (Docket # FDA-2009-D-0428)	No evidence of any response in the docket.
Sept. 12, 2010	Glen Paul Freiberg, RAC Regulatory, Clinical and Quality Consulting	Analytical Marker Tests (AMTs); Draft Guidance for Industry and FDA (Docket # FDA-2010-N-0274)[17]	No evidence of any response in the docket.
Oct. 19, 2011	mHealth Regulatory Coalition	Guidance on Regulation of mHealth Technologies (Docket # FDA-2011-D-0530)[18]	No response so far.

[13] This docket is not available on Regulations.gov. The original posting is available at: http://www.fda.gov/ohrms/dockets/dailys/03/jul03/072403/03d-0334-gdl0001-vol1.pdf.

[14] The Agency may have, at some point, sent a letter indicating a high-level response to the proposed guidance document, but we cannot confirm its existence. According to FDA's Dockets Management, there are no comments or Agency responses in this docket.

[15] This proposed guidance document was submitted under 21 C.F.R. § 10.115(f)(3) but appears to have been erroneously placed in the docket established for a notice of proposed rulemaking on which the FDA indicated that it received no comments. Orthopedic Devices; Effective Date of Requirement for Premarket Approval for Hip Joint Metal/Polymer or Ceramic/Polymer Semiconstrained Resurfacing Cemented Prosthesis, 69 Fed. Reg. 59,132, 59,133 (Oct. 4, 2004), *available at* http://www.gpo.gov/fdsys/pkg/FR-2004-10-04/pdf/04-22210.pdf.

[16] We have worked with FDA's Dockets Management but have been unsuccessful in finding the docket number for this document. This document was subsequently re-submitted as part of comments to a notice regarding the Medical Device Innovation Initiative in Docket # FDA-2011-N-0063.

[17] This document was submitted as a comment on a public meeting to address the oversight of lab-developed tests.

[18] This document was submitted as a comment on a guidance document that covers a narrower range of issues.

Researching the past guidance documents submitted to FDA was an unexpectedly difficult task. We reviewed both Regulations.gov and FDA.gov, as well as worked with FDA's Dockets Management Branch, to identify these proposed guidance documents. The first difficulty we encountered was that the FDA docket is not set up to segregate these kinds of submissions from other types of public submissions (e.g., citizen petitions or comments to Agency documents). On top of that, the FDA docket has not been fully transferred from FDA.gov to Regulations.gov. Indeed, we found some of these submitted proposed guidances scattered in strange places or, in the case of submissions we knew about independently, not found at all (even in FDA's internal Dockets Management database). Not only does this make tracking the Agency's responses rather difficult, it also does not instill confidence that FDA is actually paying attention and giving due consideration to these recommendations. The Agency needs to put these in special repositories and then manage the Agency's response.

As they are doing, FDA should want to encourage industry proposals in these days of reduced resources. When industry does a credible job, submitting a proposed guidance is a win-win in that policy is better informed and the Agency can save resources.

What FDA is not doing is acting on these proposals, and that discourages others from following suit. FDA cannot realistically expect industry groups to go through the enormous time and effort to develop and submit a proposed guidance document when they seem to generate so little response by the Agency. If FDA wants to receive more proposed guidance documents from the public, the Agency needs to do much more to show that they value the contributions. We are not at all suggesting that the Agency needs to blindly accept these guidance documents, and maybe indeed the right thing is to turn them down, but a reasoned response would go a long way to showing that the Agency values the suggestions.

b. Proposed solution

Two changes are necessary.

First, FDA should carefully track these proposals and allow other members of the public to comment. This means setting up a special intake process for Dockets Management that will appropriately segregate proposed submitted guidance documents from other submissions and allow other stakeholders to comment. These submissions need to be much more easily found than they are currently. Even just a page on an appropriate website so the public can see what has been submitted and offer their input would make the system work much better.

Second, FDA must make sure the Agency responds appropriately and timely, saying what the Agency likes and will use and what it does not like and will decline. This does not need to be long. A couple pages in a response letter may well do. People who invest a tremendous amount of time putting a submission together want some feedback to understand the Agency's thought process. The Agency may have good reasons for not accepting a proposal and knowing those reasons might help the person or organization that submitted the guidance.

2. Not Acting on Industry Comments on Guidance

Please note that this section summarizes this issue. A detailed analysis and supporting data is attached as Appendix A.

a. Problem

i. Background

By regulation, FDA is required to take serious consideration of comments submitted on proposed guidance documents (whether level 1 or 2) and make appropriate changes to the guidance before finalizing it (for level 1). Specifically, for level 1 guidance documents, 21 C.F.R. § 10.115 requires FDA to "[r]eview any comments received and prepare the final version of the guidance document that incorporates suggested changes, when appropriate . . . ."[19] A similar requirement exists for level 2 guidance, albeit after the guidance is initially published in final form.[20]

The regulations are silent, though, about any FDA responsibility for explaining its decisions regarding how it plans to address specific comments. That's not an accident; FDA designed its process that way. Ironically *in response to comments* on its good guidance practices, FDA explained:

> (Comment 12) Many comments urged us to include a provision in the regulation requiring us to provide written responses to public comments or suggestions for revising guidance documents. One comment stated that we should respond to each suggestion for a revision to an existing guidance document within 90 days. Other comments stated that we should explain to the public why we changed, or why we did not change, a guidance document between the draft and final stages. Some comments recommended that we provide general responses to comments grouped by topic. Others suggested that we be required to issue a written response when certain criteria are met (e.g., when a majority of the comments on a guidance document concern the same issue).
>
> We believe that it is in the public interest to have an efficient process for developing guidance documents. The guidance document development process would be hampered if we were required to respond to each comment. When comments received are very significant or cause us to revise a guidance, we often discuss those comments in the notice of availability (NOA) for the final guidance or in the final guidance document. We intend to continue this practice. However, making a firm commitment to provide a written response to all comments when issuing a final guidance would unnecessarily delay the issuance of the document.[21]

[19] 21 C.F.R. § 10.115(g)(1)(iv)(A).

[20] *Id.* § 10.115(g)(4)(ii).

[21] Administrative Practices and Procedures; Good Guidance Practices, 65 Fed. Reg. 56,468, 56,470 (Sept. 19, 2000), *available at* http://www.gpo.gov/fdsys/pkg/FR-2000-09-19/pdf/00-23887.pdf.

When CDRH created its *CDRH Manual For Good Guidance Practices (GGP) Regulations; Final Guidance For FDA Staff*,[22] in the template for a final level 1 guidance *Federal Register* notice of availability, CDRH expressly noted that the NOA should "address any significant comments that were received" in the background section.[23]

ii. Analysis

Unfortunately, FDA *has simply not followed through very well* with its own expressed intentions to describe the Agency's response to significant comments. In the absence of a binding requirement and in the face of competing priorities, FDA has chosen to simply release final guidance with virtually no explanation. Without any statement articulating why FDA chose to adopt or reject major themes in the comments, we are left merely to guess what the Agency thought of them. FDA often does very little in the NOA to explain the Agency's reactions to the comments, and makes very few changes when moving from the proposed to the final draft.

Please see Appendix A for an analysis of: (1) the notices of availability for final guidances where FDA received significant comments on the draft guidance, and (2) the final text of guidance documents again where significant comments were made.

b. Proposed solution

FDA should respond to the comments made in guidance development at least at a high level. Specifically, we are requesting that the Agency modify its regulations to make a commitment that the Agency will respond to any significant comments by:

- Explaining whether the Agency agrees or disagrees with the comment,
- Providing a brief summary of the basis for any disagreement, and
- Identifying what the Agency plans to do in response.

This is not rulemaking, so the response will not be the administrative record for a final Agency action and not subject to judicial review.

3. Not Allowing the Public to Participate Prior to a Proposed Guidance

a. Problem

Unfortunately, FDA sometimes ceases all substantive discussion with the public, including industry, on a topic under consideration for guidance. That should not happen and is a carryover from rulemaking. Comments have been circulating for years within FDA to the effect that those who write guidance are not supposed to engage in any oral discussions with the public while they are drafting the guidance. But even in rulemaking there is no prohibition against dialogue and collaboration, only a requirement that it needs to be documented in the administrative record.

[22] CTR. FOR DEVICES & RADIOLOGICAL HEALTH, FOOD & DRUG ADMIN., CDRH MANUAL FOR THE GOOD GUIDANCE PRACTICES (GGP) REGULATIONS; FINAL GUIDANCE FOR FDA STAFF (2001), *available at* http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070857.pdf.

[23] *Id.* at Attachment III.

There are at least two reasons for dialogue while the Agency is crafting new guidance:

- While FDA is developing new regulations, manufacturers still need to comply with existing requirements. Combination product manufacturers specifically need tools to understand the application of existing requirements to combination products, while new guidance is under development.

- Quite apart from interpreting existing guidance, FDA should affirmatively seek out public engagement in order to get the input necessary to craft a new guidance document. This is very much in alignment with the President's directive that agencies act in the open, seeking collaboration with the public during policymaking.

Documenting this is difficult because it is both informal and oral when it happens. The undersigned can personally attest to many times over the last 15 years when Agency representatives have declined to engage in substantive discussions on topics that were the subject of an ongoing effort to develop guidance, citing that ongoing effort as the reason they could not discuss the topic.

b. Proposed solution

We request that the Agency develop a guidance document for staff and industry on how to communicate during policy making. To help the Agency, we have put together a first draft, attached as Appendix C. Whether or not the Agency agrees with us on the substance, we request that the Agency address the topics that we have identified in the proposed guidance document.

Our Plan At This Juncture

Over the last few years, we have made many suggestions regarding how the Agency ought to improve its guidance development process. We filed a very substantial comment in August of 2009 in which we made eight separate recommendations for how to improve the guidance process. In this letter, we are repeating several of those, but hopefully amplifying in a way that adds value. Among other things, in this letter, we are providing a proposed draft guidance on interaction between the Agency and the public during guidance development.

Because some of what we suggest requires amending the regulations and because we are proposing a guidance document without there being any special guidance proposal process, we are going to synthesize these various recommendations in a singular citizen petition. That way, it will be easier to track the Agency's response to these recommendations.

Conclusion

As with most things in government or business today, it is not just about doing more with less, but it is about having the right priorities. We think there are very few things FDA has to do that are more important than working collaboratively with outside stakeholders to craft the most appropriate policy. We fear that with all of the competing priorities, some important stuff like

listening to stakeholders has fallen by the wayside. We ask that the importance of stakeholder engagement be brought back into focus.

Respectfully submitted,

Bradley Merrill Thompson,
On behalf of the Combination Products Coalition

cc:
Stephen Spielberg, MD, PhD, Deputy Commissioner for Medical Products and Tobacco
Jill Warner, JD, Associate Commissioner (Acting), Office of Special Medical Programs
Thinh Nguyen, Director, Office of Combination Products

Appendix A

Not Acting on Industry Comments on Guidance

This Appendix analyzes the Agency's failure to act on industry comments on guidance documents, based on: (1) the notices of availability for final guidances where FDA received there had been significant comments made on the draft guidance, and (2) the final text of guidance documents again where significant comments were made.

i. Background

As discussed in the body of these comments, by regulation, FDA is required to take serious consideration of comments submitted on proposed guidance documents (whether level 1 or 2) and make appropriate changes to the guidance before finalizing it (for level 1). Specifically, for level 1 guidance documents, 21 C.F.R. § 10.115 requires FDA to "[r]eview any comments received and prepare the final version of the guidance document that incorporates suggested changes, when appropriate . . . ."[24] A similar requirement exists for level 2 guidance, albeit after the guidance is initially published in final form.[25]

Further, when CDRH created its *CDRH Manual For Good Guidance Practices (GGP) Regulations; Final Guidance For FDA Staff*,[26] in the template for a final level 1 guidance *Federal Register* notice of availability, CDRH expressly noted that the NOA should "address any significant comments that were received" in the background section.[27]

ii. Analysis

Unfortunately, FDA *has simply not followed through very well* with its own expressed intentions to describe the Agency's response to significant comments. In the absence of a binding requirement and in the face of competing priorities, FDA has chosen to simply release final guidance with virtually no explanation. Without any statement articulating why FDA chose to adopt or reject major themes in the comments, we are left merely to guess what the Agency thought of them.

Let's look at the evidence. We decided to look at two different data sources: (1) the notices of availability for final guidances where FDA received significant comments on the draft guidance, and (2) the final text of guidance documents again where significant comments were made. The former tells us whether FDA is taking the time to explain their reaction to comments, and the latter suggests just how comprehensively FDA is acting on the comments.

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[24] 21 C.F.R. § 10.115(g)(1)(iv)(A).

[25] *Id.* § 10.115(g)(4)(ii).

[26] CTR. FOR DEVICES & RADIOLOGICAL HEALTH, FOOD & DRUG ADMIN., CDRH MANUAL FOR THE GOOD GUIDANCE PRACTICES (GGP) REGULATIONS; FINAL GUIDANCE FOR FDA STAFF (2001), *available at* http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070857.pdf.

[27] *Id.* at Attachment III.

To start, we searched the public docket for all guidance documents, reviewing over 200 guidance documents produced by CDRH since 1991.[28] We used the number of comments as a sort of barometer of the seriousness of the comments, although we recognize that the approach is only an estimation. We then supplemented that analysis by looking at guidance documents that were developed across multiple Centers, thinking that many of them may deal with some of the more important issues.

1. Description of Significant Comments in NOAs

We looked at several of the NOAs for those guidance documents for which FDA has published a final guidance and we are concerned that the Agency has responded inadequately to these comments. Take, for example, the *Guidance for Industry: Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices*.[29] The public submitted over 100 sets of comments, including the following examples:

- **Blue Cross and Blue Shield Association (BCBSA)** stated: "Our concerns are centered on patient safety, which we feel will be unintentionally threatened by the recommendations outlined in this draft language. . . . [T]he guidelines do not currently do enough to address the variation in quality that exists in peer-reviewed literature. . . . Finally, we do not feel that the provisions suggested in the draft guidance would deliver more accurate and timely information on off-label drug use than the current peer-to-peer and professional information streams. . . . BCBSA supports the use of independent objective sources to provide the analyses and distribution of information on drugs to health professionals, particularly in the area of off-label usage."

- In requesting that FDA remove the requirement that articles be disseminated with representative publications that reach contrary or different conclusions regarding an unapproved use, **Sanofi Aventis** stated: "There are instances where information containing contrary or different conclusions would not have the same level of value. . . . [For example,] when a follow-up publication is of superior quality, . . . the contrary or different conclusion may become moot. Furthermore, drawing conclusions from study-to-study comparisons, which may contain a myriad of potential differences . . . is not always an accurate or appropriate method for obtaining the necessary information."

- **Consumers Union (CU)** commented: "While CU recognizes that physician prescribing for off-label uses can be beneficial to the patient, manufacturer promotion of off-label use is not in the best interest of the patient. . . . A physician's risk-benefit assessment in prescribing a medication for an unapproved indication should rely on her professional judgment, not manufacturer-influenced or incomplete studies of effectiveness. By allowing manufacturers to market off-label use based on peer-reviewed articles instead of FDA approval and adequate and well-controlled studies, the [draft guidance]

[28] We picked CDRH because they had been prolific in the production of guidance documents, and also because they had been very specific in their template about addressing comments in the final NOA.

[29] OFFICE OF THE COMM'R, U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: GOOD REPRINT PRACTICES FOR THE DISTRIBUTION OF MEDICAL JOURNAL ARTICLES AND MEDICAL OR SCIENTIFIC REFERENCE PUBLICATIONS ON UNAPPROVED NEW USES OF APPROVED DRUGS AND APPROVED OR CLEARED MEDICAL DEVICES (2009), *available at* http://www.regulations.gov/#!documentDetail;D=FDA-2008-D-0053-0127.

inappropriately discourages manufacturers from conducting adequate and well-controlled studies for new indications. Peer-reviewed medical and scientific journals vary widely in quality and scientific integrity. The [draft guidance]'s recommendation that a distributed supplement should not be funded or influenced by a manufacturer is insufficient to protect against industry 'ghostwriting' or coauthoring, a common occurrence that is very difficult to trace due to voluntary conflict of interest policies and little enforcement."

- **Medical Device Manufacturers Association** stated: "Although the Federal Food, Drug and Cosmetic Act (the "FDCA") and its implementing regulations generally prohibit manufacturers from promoting or advertising an approved or cleared device for an unapproved, or off-label, use, these prohibitions are subject to the manufacturers' First Amendment rights to disseminate truthful, non-misleading information regarding their products. Moreover these prohibitions do not restrict a physician's off-label use of a product in his or her practice of medicine. . . . In order to fully assess the benefits and risks of utilizing a product off-label, physicians and patients must have access to truthful and non-misleading information regarding the product and its uses. . . . [Therefore, t]he final guidance should provide an unqualified safe harbor that does not limit a manufacturer's first amendment rights or other permissible mechanisms for distributing truthful and non-misleading information regarding off-label uses. . . . The final draft [sic] guidance should not unduly restrict the types of scientific information which are covered by the safe harbor."

Despite the number, diversity, and significance of the public comments, when the Agency announced the availability of the final guidance, FDA simply characterized the numerous comments as "several" and offered a one-paragraph, high-level summary of the comments and the changes implemented.[30] The following is the extent to which the Agency discussed the public comments:

> Some of the changes made to the guidance based on comments received, and on FDA's own initiative, include a specific reference encouraging manufacturers to seek approvals and clearance for new indications and intended uses for medical products. FDA recognizes the value of new indications and uses for approved products and wants these to be studied so that patients and healthcare professionals receive safe and effective treatments. Many comments suggested that FDA continue to require presubmission of the articles and suggested other mandatory review practices. However, given the sunset of section 401 of FDAMA these were not within FDA's authority and thus outside the scope of this guidance. Section IV of the guidance clarifies a number of bullet points to address comments expressing confusion as to some of the terms and practices expressed. Additional

[30] Guidance for Industry on Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices; Availability, 74 Fed. Reg. 1694, 1694 (Jan. 13, 2009), *available at* http://www.gpo.gov/fdsys/pkg/FR-2009-01-13/pdf/E9-452.pdf.

> information was provided to distinguish the dissemination of these types of articles from other industry practices.[31]

Apparently some of the changes (it is not clear which) were Agency-initiated after publication of the draft guidance and were implemented without public consideration. Furthermore, it is not clear from this statement in the NOA what FDA thought of any of the public comments. For example, we cannot tell how the Agency took into account BCBSA's concern about variation in the quality of peer-reviewed journals, or Sanofi Aventis' concern that disseminating articles with contrary or different conclusions may have a deleterious effect on patient care, or Consumers Union's concern about ghostwriting, or MDMA's concern about the manufacturer's first amendment rights. All of these are valid concerns and warrant meaningful and transparent consideration from the Agency.

Let's take another example: the *Guidance for Industry and Food and Drug Administration Staff: Impact Resistant Lenses: Questions and Answers*.[32] In response to the draft guidance, FDA received 56 sets of comments from the public. Here are just a couple:

- **National Association of Optometrists and Opticians, Inc. (NAOO)** commented: "The NAOO respectfully opposes the revisions contemplated by this document for the following reasons: The empirical evidence justifying many of the proposed revisions is, in our judgment simply inadequate; . . . The [existing] rule has successfully protected American consumers since its inception and we are unaware of the rationale for justifying any significant revisions to the current standard; . . . . Retail optical stores and others who perform lens edging tasks will be, for the first time, classified as 'manufacturers' and be required to perform the impact resistant test on their premises; [and] Vision care consumers who need new eyewear due to emergencies like lost or broken eyeglasses (frames or lenses) will be inconvenienced by delays in receiving their new eyewear since vision care professionals and retail stores will be required to use wholesale laboratories rather than performing such tasks and functions on their respective premises . . . ."

- **The Vision Council** commented: "We share the FDA's interest in developing updated Q&A guidelines which will assist the optical community in providing safe lens products to the American consumer. However, we do not believe that the FDA Draft Guidelines . . . reflects the current needs of the optical community or, in some cases, the meaning and intent of 21 CFR 801.410. As such we are offering for your consideration a revision of the FDA Draft Q&A. Our revised Draft . . . represents the efforts of technical experts from the lens manufacturer, optical laboratory, ophthalmology, optometry and opticianary segments of the optical industry. . . . We feel it is very important that the FDA takes action in a reasonable period of time . . . ."

Yet, when the Agency finalized the document, the NOA makes no mention of the concern that the basis for the guidance document is inadequate, the impact on small retailers of becoming

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[31] *Id.*

[32] CTR. FOR DEVICES & RADIOLOGICAL HEALTH, U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY AND FDA STAFF: IMPACT-RESISTANT LENSES: QUESTIONS AND ANSWERS (2010), *available at* http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070755.pdf.

regulated as a device manufacturer, or the risk to the consumer in emergency situations where lenses are needed. Instead, FDA simply stated the following:

> FDA received numerous comments from laboratories, trade associations, retail establishments, and consumers surrounding three main issues. FDA further clarified the definition of "manufacturer" according to the Quality System regulation (21 CFR 820.3(o)). Additionally, based on data provided in the comments, FDA eliminated a question regarding the salability of plastic prescription lenses tested as part of a statistical sample. FDA also modified several questions which had indicated that the testing of all lenses had to be done after edging to clarify that all plastic prescription lenses and glass over-the-counter lenses could be tested in either "un-cut finished" or "finished" form.[33]

Here's yet another example: the *Guidance for Industry: Current Good Tissue Practice (CGTP) and Additional Requirements for Manufacturers of Human Cells, tissues, and Cellular and Tissue-Based Products (HCT/Ps).*[34] The Agency received 28 sets of comments, including the following:

- **The American Academy of Orthopaedic Surgeons** stated: "Recommendations in the document state that in order to adequately audit a supplying tissue procurement agency, the next of kin should be contacted to assure the accuracy of provided information. This would, in fact mean that the recovery agency would have to reconnect with the donor family, requiring them to undergo some process of repeat questioning, which is inappropriate and intrusive, especially during a time of bereavement. In addition, the criteria for the audits are much too broad and nonspecific. There should be explicit language outlining what will be audited (appropriate storage temperatures, records, testing information, proper storage, equipment, recovery process measures, facility upkeep)."

- **The American Red Cross** commented: "The Red Cross fully supports the intent of the draft guidance to prevent the introduction, transmission, or spread of communicable diseases by HCT/Ps. . . .While we agree with many of the stated requirements given in the draft guidance, we offer the following comments for your consideration. . . . Section H . . . states: 'A controlled environment, such as an operating room setting is recommended but not required…' This example is unrealistic and impractical as no hospital or other similar facility would provide such a resource for stem cell harvesting."

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[33] Guidance for Industry and Food and Drug Administration Staff; Impact-Resistant Lenses: Questions and Answers; Availability, 75 Fed. Reg. 53,971, 53,971 (Sept. 2, 2010), *available at* http://www.gpo.gov/fdsys/pkg/FR-2010-09-02/pdf/2010-21908.pdf.

[34] CTR. FOR BIOLOGICS EVALUATION & RESEARCH, FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: CURRENT GOOD TISSUE PRACTICE (CGTP) AND ADDITIONAL REQUIREMENTS FOR MANUFACTURERS OF HUMAN CELLS, TISSUES, AND CELLULAR AND TISSUE-BASED PRODUCTS (HCT/PS) (2011), *available at* http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM285223.pdf.

As opposed to addressing these and many other important public comments, FDA merely stated the following in the NOA for the final guidance:

> FDA received numerous comments on the draft guidance, and those comments were considered as the guidance was finalized. In addition, editorial changes were made to improve clarity.[35]

That pretty much speaks for itself. This type of response is simply unacceptable and does not do justice to the tremendous effort that goes into developing comments to these Agency documents—documents that are vital to the public's understanding of FDA guidance.

2. Changes to Final Guidances When Significant Comments Are Made

Just to recap, there are two ways that we on the outside can see what FDA does with our comments:

- In the notice of availability, we can read about FDA's high-level reaction to the comments, and perhaps especially the comments that the Agency rejects; and
- In the guidance document itself, we can read what the FDA has changed on the basis of the comments.

Having established that FDA often does very little in the NOA to explain the Agency's reactions to the comments, we turn to the guidance documents themselves. Our concern is that FDA makes very few changes when moving from the proposed to the final draft.

Appendix B includes a redlined copy of the *Guidance for Industry: Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices*.[36] As we have already explained, the Agency received well over 100 comments, and many of them were very lengthy and substantive. Appendix B shows that the Agency in response to all of those comments made a handful of very minor editorial changes to the document.

More generally, if we look at the same examples as discussed in the previous section, we see that the final guidance documents failed to address the vast majority of the comments in any meaningful way. Of the randomly selected comments that we listed above, the Agency addressed only one. Here's a summary of what we found.

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[35] Guidance for Industry: Current Good Tissue Practice and Additional Requirements for Manufacturers of Human Cells, Tissues, and Cellular and Tissue-Based Products; Availability, 76 Fed. Reg. 82,308, 82,308 (Dec. 30, 2011), *available at* http://www.gpo.gov/fdsys/pkg/FR-2011-12-30/pdf/2011-33572.pdf.

[36] OFFICE OF THE COMM'R, U.S. FOOD & DRUG ADMIN., *supra* note **Error! Bookmark not defined.**.

Guidance Document	Commenter	Evidence of Consideration in Final Guidance
Guidance for Industry: Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices	Blue Cross and Blue Shield Association	• The final guidance expanded the types of clinical studies that can be used, but there is no change that addresses the concern for the variations in quality of peer-reviewed literature. • There is no discussion of the concern that the guidance fails to deliver accurate and timely information on off-label drug use. • There is no discussion of the need for independent objective sources.
	Sanofi Aventis	• The final guidance added language regarding contradictory studies, but failed to address concerns that presenting contradictory studies may not add value due to the difficulty of making study comparisons.
	Consumer Union	• The final guidance fails to address the concern that it discourages manufacturers from conducting adequate and well-controlled studies for new indications. • The final guidance does not address the concern that ghostwriting may continue despite the guidance.
	Medical Device Manufacturers Association	• The final guidance neither establishes a safe harbor for first amendment rights nor addresses the associated concerns.
Guidance for Industry and Food and Drug Administration Staff: Impact Resistant Lenses: Questions and Answers	National Association of Optometrists and Opticians, Inc.	• The final guidance makes no attempt to explain the basis for the revisions to the then-existing standard or to justify its decision to ignore such a concern. • The final guidance clarified the manufacturer's requirements but failed to address the concerns that many small businesses would be impacted by being regulated as a manufacturer. • The final guidance does not address concerns associated with emergency situations.
	The Vision Council	• The final guidance does not address the concern that the Agency's current thinking (as demonstrated in the guidance) fails to reflect the current needs of the optical community or the meaning and intent of the regulations. • There is no evidence that FDA considered the revised draft guidance that was submitted.
Guidance for Industry: Current Good Tissue Practice (CGTP) and Additional Requirements for Manufacturers of Human Cells, tissues, and Cellular and Tissue-Based Products (HCT/Ps)	The American Academy of Orthopaedic Surgeons	• The final guidance removed the "next of kin" provision. • The final guidance made no changes in response to the specific request for an explicit list of what should be audited.
	The American Red Cross	• The final guidance did not change this provision and failed to address the concern that it is unrealistic and impractical.

The point of our analysis is not to address the merits of the comments or to judge the Agency's decision to make changes or not to a particular guidance. On the contrary, we use this analysis to

illustrate that FDA too often fails to act on the vast majority of these public comments, which would be okay of the agency articulated its reasons for rejecting them. But to neither act on them nor explain why the agency is rejecting them makes the guidance process neither participatory nor collaborative.

There is a third like to the stool that is equally concerning. In addition to not making changes and not explaining why the agency rejects a particular comment, the agency all too often simply does not move the guidance development process forward in any way. In our 2009 comments referenced above, we explained the statistical analysis we did of the number of times that draft guidances were simply left in draft form, not finalized. By leaving guidance documents in draft form indefinitely, the result is the same as not responding to the comments that were submitted. In the last month or so we have heard agency officials express an intention to correct this in the future, and we applaud that initiative and look forward to seeing it in action.

Of course, this issue is not limited to comments on final guidance, but comments on more open-ended questions and reports that FDA periodically publishes. For example, on August 7, 2009, we filed extensive comments in this exact same docket on ways to improve the guidance development process. In 2011, FDA published two different broad white papers on the topic of guidance for industry, and the Agency did not incorporate, address, or even acknowledge **any** of the ideas we had developed.[37] An example of an idea that FDA should have seriously considered

[37] We did notice, though, that FDA published a broad summary of some of the comments submitted to the transparency docket relating to guidance documents. That summary explained:

> Many comments from industry stated that improvements are needed to the agency's guidance development process. Several comments stated the timeliness of the process must be improved, noting that "the process moves too slowly to provide meaningful information to industry." Some comments suggested that FDA formally track the agency's progress in drafting guidance documents, and include clear timelines and specific development stages. Comments further noted that if the guidance development process is delayed, stakeholders should be notified. Industry also requested that FDA inform stakeholders about the priority of guidances that the agency is planning on working on during the year.
>
> Comments suggested that FDA create more opportunities for feedback from stakeholders during the guidance development process, including outside of the formal notice and comment mechanism. Comments suggested that once the agency receives input on a draft guidance document, FDA establish a transparent procedure for describing how it has evaluated those comments.
>
> Comments suggested that for guidance documents that have been in draft form for a specified period of time, e.g., longer than five years, FDA should reissue the guidance for public comment, so that the final draft reflects the most current knowledge of the subject matter and the guidance continues to be relevant. Comments also requested that FDA develop and communicate a work plan to finalize guidance that has been in draft form for many years.
>
> Comments suggested that training and education should be part of the agency's guidance implementation process. Suggestions included holding public workshops where FDA employees review new guidances, holding webinars that allow for open public participation, and issuing question and answer documents about the guidance. Comments noted that training should occur early in the implementation process, preferably soon after a new policy or process is

is the suggestion that FDA solicit input from industry on the scope of a guidance document before drafting it, to ensure that the Agency addresses the open questions, as well as all of the topics covered in this comment letter.

While responding to comments in the context of informal rulemaking is mandatory, courts have been careful to point out the underlying benefits such responses produce. These benefits are present in the guidance development process just as much as they are in rulemaking. Written responses to comments help by:

- Further explaining and amplifying the meaning of the guidance. Basically the comments and responses become an informal question-and-answer session that helps explain the guidance.

- Providing internal Agency discipline to make sure the Agency has indeed thought about the comments.[38] Agencies are big organizations, and it is easy to assume that someone has thought seriously about the comments and made appropriate changes. But that's not always true.

- Creating a sense of fairness among those regulated—that the Agency listened and took their concerns into account. While fairness is perhaps an intangible benefit, it is important to our democratic society and it also increases compliance. When the regulated community believes that a requirement is fair, that perception makes it easier for the regulated organization to get its employees to comply voluntarily. The bottom line is that time invested in presenting guidance as fair produces greater compliance which in turn better protects the health and safety of the American public.

- Encouraging future comments. The response is a reward and show of respect that will encourage the public to comment in the future. No one likes to waste their time, and if the public feels as though their comments are being ignored, they will not invest the time to comment further. President Obama values public input, so it's important for the agencies under his command to encourage that input and to display openness.

To put it a somewhat different way, one court has ruled that the opportunity to comment "is meaningless unless the Agency responds to specific points raised by the public."[39]

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implemented.

Comments also requested that FDA issue more guidance documents.

U.S. Food & Drug Admin., About FDA: Guidance Development—Summary of Public Comments, http://www.fda.gov/AboutFDA/Transparency/TransparencytoRegulatedIndustry/PhaseIIITransparencyReport/ActionItemsandDraftProposalsbyTopicArea/ucm238976.htm (last visited Feb. 16, 2012).

[38] *See* Dry Colors Mfrs. Ass'n v. Dep't of Labor, 486 F.2d 98, 105 (3d Cir. 1973) (stating that requirement for statement of basis and purpose "provides an internal check on arbitrary agency action by ensuring that prior to taking action and agency can clearly articulate the reasons for its decision.").

[39] Alabama Power Co. v. Costle, 636 F.2d 323, 384 (D.C.Cir. 1979)

We are, though, sympathetic to FDA's challenges. As we have noted a couple of times in this letter, we understand the Agency facings competing priorities and constrained resources. While, as outsiders, we do not know the internal procedures intimately for revising and publishing final guidance, we can imagine that the more editing that is done to propose guidance, the more work that is required for the necessary consensus building to seek approval for the revised guidance. But even though such revisions add significant work, undertaking those revisions is essential to produce the best policy to serve both the agency and the public.

While it is not a complete solution, we would like to point out that there is a tremendous difference between the concise statement of basis and purpose in rulemaking and an explanation of the Agency's response to comments that we are requesting in guidance. The former becomes the basis for judicial review of a final Agency action, while the latter serves no such purpose. Guidance documents are generally not final Agency actions and are not intended to be judicially reviewable. As a result, the tremendous amount of time it takes the Agency to draft a statement of basis and purpose in rulemaking is not required to draft a brief summary of the principal comments made during guidance development. The brief summary done for guidance need not be as carefully, comprehensively, or defensively written. It just needs to candidly reveal the Agency’s thought process as the Agency reacts to comments.

Further, for those regulatory pronouncements that do not require public input, CDRH at least has developed a mechanism to send out industry letters that make unilateral announcements. So where public input is not desired, there are quick and efficient means for distributing that information.

As a result, our request for a narrative explanation of the agency's response to comments should not slow down the guidance development process at all.

c. Proposed solution

FDA should respond to the comments made in guidance development at least at a high level. Specifically, we are requesting that the Agency modify its regulations to make a commitment that the Agency will respond to any significant comments by:

- Explaining whether the Agency agrees or disagrees with the comment,
- Providing a brief summary of the basis for any disagreement, and
- Identifying what the Agency plans to do in response.

This is not rulemaking, so the response will not be the administrative record for a final Agency action and not subject to judicial review.

Appendix B

GUIDANCE FOR INDUSTRY
Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices

U.S.

Department of Health and Human Services
Food and Drug Administration
Office of the Commissioner,
Office of Policy
January 2009

Guidance for Industry~~:~~

Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices

This ~~*draft*~~ guidance document represents the Food and Drug Administration's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You may use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, please contact the appropriate FDA staff.

I. Introduction

This ~~draft~~ guidance is intended to describe the Food and Drug Administration's (FDA or Agency) current thinking regarding "Good Reprint Practices" with regard to the distribution by a drug or medical device manufacturer (or representative)[1] of medical journal articles and scientific or medical reference publications (referred to generally as medical and scientific information) that discuss unapproved new uses[2] for approved drugs[3] or approved or cleared medical devices marketed in the United States to healthcare professionals and healthcare entities.[4]

FDA's guidance documents~~, including this draft guidance,~~ do not establish legally enforceable rights or responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. Background

Section 401 of the Food and Drug Administration Modernization Act (FDAMA) (21 U.S.C. § 360aaa, § 551, Federal Food, Drug, and Cosmetic Act (FD&C Act~~)~~)), described certain conditions under which a drug or medical device manufacturer could choose to disseminate medical and scientific information discussing unapproved uses of approved drugs and cleared or approved medical devices to healthcare professionals and certain entities (including pharmacy benefits managers, health insurance

issuers, group health plans, and Federal or State governmental agencies). FDAMA section 401 provided that, if these conditions were met, dissemination of such journal articles or reference publications would not be considered as evidence of the manufacturer's intent that the product be used for an unapproved new use. FDA implementing regulations were codified at 21 C.F.R. FR Part 99.

In 2000, subsequent to a decision by the United States Court of Appeals for the District of Columbia Circuit, FDA published a Notice (65 Fed. Reg. 14286, March 16, 2000) clarifying the applicability of the FDAMA section 401 provision and the FDA implementing regulations. In that Notice, FDA stated that the statute and implementing regulations constituted a "safe harbor" for a manufacturer that complies with them before and while disseminating journal articles and reference publications about "unapproved new uses" of approved or cleared products. If a manufacturer complied with the FDAMA provision, the distribution of such journal articles or reference publications would not be used as evidence of an intent that the product distributed by the manufacturer be used for an unapproved use. The Notice also stated that if a manufacturer chose to disseminate materials but not proceed under FDAMA section 401, that failure would not constitute an independent violation of law. but could be used as evidence of a manufacturer's intent that the product be used for an unapproved use.

FDAMA section 401 ceased to be effective on September 30, 2006, and the implementing regulations are no longer applicable. In light of the statute's sunset, FDA is providing its current views on the dissemination of medical journal articles and medical or scientific reference publications on unapproved uses of approved drugs and approved or cleared medical devices to healthcare professionals and healthcare entities.

III. Purpose

As explained in FDA's March 16, 2000 Notice, the FD&C Act and FDA's implementing regulations generally prohibit manufacturers of new drugs or medical devices from distributing products in interstate commerce for any intended use that FDA has not approved as safe and effective or cleared through a substantial equivalence determination. (E (e.*g.*, FD&C Act §§ 505(a), 502(o), 501(f)(1)(B), 301(a) and (d); 21 U.S.C. §§ 355, 352(o), 351(f)(1)(B), 331(a) and (d)). The Agency recognizes the value of having new indications and intended uses for products approved or cleared by FDA and encourages sponsors of medical products to seek such approvals or clearances. An approved new drug that is marketed for an unapproved use becomes misbranded and is an unapproved new drug with respect to that use. (FD&C Act §§ 505(a), 301(d), 21 U.S.C. 355(a), 331(d)). An approved drug that is marketed for an unapproved use (whether in labeling or not) is misbranded because the labeling of such drug does not include "adequate directions for use" (FD&C Act § 502(f); 21 U.S.C. § 352(f); 21 CFR 201.100(c)(1)). Similarly, a medical device that is promoted for a use that has not been approved or cleared by FDA is adulterated and misbranded.

FDA does recognize, however, recognize the important public health and policy reasons for allowing manufacturers to disseminate justification supporting dissemination of truthful and non-misleading medical journal articles and medical or scientific reference publications on unapproved uses of approved drugs and approved or cleared medical devices to healthcare professionals and healthcare entities. Once a drug or medical device has been approved or cleared by FDA, generally, healthcare professionals may lawfully use or prescribe that product for uses or treatment regimens that are not included in the product's approved labeling (or, in the case of a medical device cleared under the 510(k) process, in the product's statement of intended uses). These off-label uses or treatment regimens may be important and may even constitute a medically recognized standard of care. Accordingly, the public health may be advanced by healthcare professionals' receipt of medical

journal articles and medical or scientific reference publications on unapproved ~~or~~ new uses of approved or cleared medical products that are truthful and not misleading.

FDA's legal authority to determine whether distribution of medical or scientific information constitutes promotion of an unapproved ~~"~~"new use~~,"~~," or whether such activities cause a product to ~~be misbranded or adulterated~~violate the FD&C Act has not changed. In recognition of the public health value to healthcare professionals of receiving truthful and non-misleading scientific and medical information, FDA is providing recommendations concerning ~~"~~"Good Reprint Practices~~"~~" for the dissemination of medical journal articles and medical or scientific reference publications on unapproved uses of drugs and medical devices.[5]

IV. Agency Recommendations for Good Reprint Practices

Scientific and medical information that concerns the safety or effectiveness of an approved drug or approved or cleared medical device for ~~a~~an unapproved new use that is not included in the product's approved labeling or statement of intended uses (including unapproved ~~or~~ new uses of approved drugs and approved or cleared devices) is often published in journal articles or reference publications. These publications are often distributed by manufacturers to healthcare professionals or healthcare entities. When a manufacturer disseminates such medical and scientific information, FDA recommends that the following principles of ~~"~~"Good Reprint Practices~~"~~" be followed.

A. Types of Reprints/Articles/Reference Publications

A scientific or medical journal article that is distributed should:

- be published by an organization that has an editorial board that uses experts who have demonstrated expertise in the subject of the article under review by the organization and who are independent of the organization to review and objectively select, reject, or provide comments about proposed articles~~,~~; and that has a publicly stated policy, to which the organization adheres, of full disclosure of any conflict of interest or biases for all authors, contributors, or editors associated with the journal or organization;
- be peer-reviewed and published in accordance with the peer-review procedures of the organization; and
- not be in the form of a special supplement or publication that has been funded in whole or in part by one or more of the manufacturers of the product that is the subject of the article.

A scientific or medical reference publication that is distributed should not be:

- primarily distributed by a drug or device manufacturer, but should be generally available in bookstores or other independent distribution channels (e.g. subscription, Internet) where medical textbooks or periodicals are sold;
- written, edited, excerpted, or published specifically for, or at the request of, a drug or device manufacturer; or
- edited or significantly influenced by a drug or device manufacturer or any individuals having a financial relationship with the manufacturer.

The information contained in the ~~above~~ scientific or medical journal article or reference publication~~s~~ should address adequate and well-controlled clinical investigations that are considered scientifically sound by experts with scientific training and experience to evaluate the safety or effectiveness of the

drug or device[4] ~~.~~ . These can include historically controlled studies, pharmacokinetic (PK) and pharmacodynamic (PD) studies, and meta-analyses if they are testing a specific clinical hypothesis.[6]

The information must not:

- be false or misleading~~, such as a~~ . For example, a distributed journal article or reference text ~~that is inconsistent with~~ should not be characterized as definitive or representative of the weight of credible evidence derived from adequate and well-controlled clinical investigations ~~(e.g., where~~if it is inconsistent with that weight of credible evidence or a significant number of other studies contradict the article or reference text's conclusions~~), that has~~; should not have been withdrawn by the journal or disclaimed by the author~~, or that discusses~~; and should not discuss a clinical investigation where FDA has previously informed the company that the clinical investigation is not adequate and well-controlled; or
- pose a significant risk to the public health, if relied upon.

The following publications are examples of publications that would not be considered consistent with the "Good Reprint Practices" outlined in this ~~draft~~ guidance:

- letters to the editor;
- abstracts of a publication;
- reports of Phase 1 trials in healthy subjects; or
- reference publications that contain little or no substantive discussion of the relevant investigation or data.

B. Manner in which to Disseminate Scientific and Medical Information

Scientific or medical information that is distributed should:

- be in the form of an unabridged reprint, copy of an article, or reference publication;
- not be marked, highlighted, summarized, or characterized by the manufacturer in any way (except to provide the accompanying disclosures discussed in this section);
- be accompanied by the approved labeling for the drug or medical device;
- be accompanied, when such information exists, by a comprehensive bibliography of ~~-~~publications discussing adequate and well-controlled clinical studies published in ~~a~~ medical journals or medical or scientific ~~text that have been previously published~~ texts about the use of the drug or medical device covered by the information disseminated (unless the information already includes such a bibliography);
- ~~in cases where the conclusions of article or text to be disseminated have been specifically called into question by another article(s) or text(s),~~ be disseminated with a representative publication, when such information exists, that reaches contrary or different conclusions regarding the unapproved use; especially those in cases where the conclusions of articles or texts to be disseminated have been specifically called into question by another published article(s) or text(s); and
- be distributed separately from information that is promotional in nature.~~-~~ For example, if a sales representative delivers a reprint to a physician in his office, the reprint should not be physically attached to any promotional material the sales representative uses or delivers during the office visit and should not be the subject of discussion between the sales representative and the physician during the sales visit.[7] Similarly, while reprints may be distributed at medical or scientific conferences in settings appropriate for scientific exchange, reprints should not be distributed in promotional exhibit halls or during promotional speakers' programs.

The journal reprint or reference publication should be accompanied by a prominently displayed and permanently affixed statement disclosing:

- that the uses described in the information have not been approved or cleared by FDA, as applicable to the described drug or medical device;
- the manufacturer's interest in the drug or medical device that is the subject of the journal reprint or reference text;
- any author known to the manufacturer as having a financial interest in the product or manufacturer or who is receiving compensation from the manufacturer, ~~if applicable;~~along with the affiliation of the author, to the extent known by the manufacturer, and the nature and amount of any such financial interest of the author or compensation received by the author from the manufacturer;[8]
- any person known to the manufacturer who has provided funding for the study~~, if applicable~~; and
- ~~any~~all significant risks or safety concerns known to the manufacturer concerning the unapproved use that are not discussed in the journal article or reference text.

V. Summary

FDA recognizes that the public health can be served when health care professionals receive truthful and non-misleading scientific and medical information on unapproved uses of approved or cleared medical products. Accordingly, if a manufacturer follows the recommendations described in Section IV of this ~~draft~~ guidance ~~and there is no unlawful promotion of the product~~, FDA does not intend to ~~use~~consider the distribution of such medical and scientific information in accordance with the recommendations in this guidance as ~~evidence of an~~establishing intent ~~by the manufacturer~~ that the product be used for an unapproved new use.[9] However, if a manufacturer engages in other conduct that unlawfully promotes an unapproved use of a medical product -- whether or not the manufacturer also engages in conduct in conformance with the recommendations in this guidance -- such other conduct may result in enforcement action.

Footnotes

[1] As used in this ~~draft~~ guidance, the term ~~"drug" includes biological products licensed under Section 351(a) of the Public Health Service Act. See 42 U.S.C. § 262(j).~~

"manufacturer" means a person who manufactures a drug or device or who is licensed by such person to distribute or market the drug or device. The term may also include the sponsor of the approved, licensed, or cleared drug or device.

[2] The terms "unapproved new use", "unapproved use", and "off-label use" are used interchangeably in this guidance to refer to a use of an approved or cleared medical product that is not included in the product's approved labeling or statement of intended uses.

[3] As used in this guidance, the terms "drug" and "device" includes biological products licensed under Section 351(a) of the Public Health Service Act. *See* 42 U.S.C. § 262(j).

[4] "Healthcare entity" includes hospitals, professional medical organizations, drug formulary committees, and health plans.

[5] FDA has elsewhere stated its views on the dissemination of information regarding unapproved uses in response to ~~unsolicited~~ requests for scientific or medical information ~~from~~ initiated solely by health care professionals. ~~See~~ Such prior FDA statements include: 62 Fed. Reg. 64073, 64086, 64091(December 3, 1997), Guidance for Industry, *Industry-Supported Scientific and Educational Activities*, (November 1997) at 64099, available at http://www.fda.gov/cder/guidance/isse.htm and 59 Fed. Reg. 59820, 59823 (November 18, 1994).

[6] In the case of medical devices, journal articles or reference publications discussing significant non-clinical research may be consistent with this ~~draft~~ guidance.

[7] To the extent that the recipients of such information have questions, the ~~Agency recommends that the~~ sales representative should refer such questions to a medical/scientific officer or department (see footnote 5), and ~~that~~ the officer or department to which the referral is made should be separate from the sales and/or marketing departments.

[8] For purposes of this recommendation, an "author" includes any individual, whether credited in the publication or not, who meets the standards for authorship set forth in the guidelines of the International Committee on Medical Journal Editors' *Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication*, section II.A.

[9] Given the sunset of FDAMA § 401, the other elements that comprised § 401 which are not specifically described in this ~~draft~~ guidance are no longer applicable.

Appendix C
Proposed Guidance on
Agency and Industry Communication on Policy Issues

Background

In addition to enforcing the law, one of the Food & Drug Administration's ("FDA's") most important roles is developing policy within the confines of the statutes laid out by Congress. But sound policy is never developed in a vacuum. Instead, developing policy often requires extensive outreach to collect the information necessary to make logical and well-supported judgments. Ordinarily that outreach should include soliciting stakeholder views to ensure both (1) that the Agency has been rigorous and comprehensive in considering all the different policy options, and (2) that the resulting policy will be embraced by those who must comply.

So how can the Agency effectively and efficiently reach out to industry, healthcare providers, patients and others to devise the most appropriate policies? Both from the standpoint of efficiency and the desire to identify the best policy options, early collaboration between the Agency and stakeholders, even before pen is ever put to paper, seems important. Independent analysis by the Agency and various stakeholder groups that is only brought together at the end is not likely to yield the most thoughtful and creative policy. But how should that early collaboration occur?

The answer to that question can be quite complex because of another concern: policymaking is often best done in the open. As Americans, we don't like the idea that special interests could form relationships with regulators to influence policy outside public scrutiny. Further, when there are competing interests at stake, both sides want to be able to respond to what the other says. That can only happen if communication is open.

So, we have one set of laws that require agencies to solicit input from the outside world when making policy, and we have another set of laws requiring that the federal government operate in the sunshine. Unfortunately, sometimes those two sets of laws clash when the sunshine laws make it very difficult—practically speaking—for regulators to obtain effective public input.

This paper seeks to answer the question of how industry and FDA can work together to develop sound policy in that legal environment.

Overview of Legal Landscape

FDA develops and expresses polices through rulemaking when the Agency wants the resulting policy to have the force of law and through the Good Guidance Practices ("GGPs") when the Agency does not need the policy to have that force. Having "the force of law," in this context, means that FDA can enforce the policy in court. Since a guidance document is not enforceable, to win a decision in court, FDA must rely on Congressional statutes and Agency regulations when it is in that forum.

To develop either a regulation or guidance, FDA must employ a public, consultative process. The rulemaking process is more formal and rigorous than guidance development because of the greater legal significance associated with rulemaking. We'll outline both processes at a high level.

Rulemaking

When discussing rulemaking, we need to be clear about the type of rulemaking at issue. There are two basic flavors—so-called "formal" and "informal." Because of the complexity of formal rulemaking, FDA almost never employs it. Formal rulemakings require the Agency to conduct what amounts to a public, trial-type hearing, using certain rules of evidence. Occasionally Congress requires that the Agency employ formal rulemaking, but more often the statute allows FDA to use informal rulemaking.

Informal rulemaking—sometimes referred to as notice and comment rulemaking—requires the Agency to publish a proposed rule in the *Federal Register*, solicit comments from the public, and then publish a final rule that includes an explanation of how the Agency addressed the comments. Because the vast majority of FDA rulemakings are informal, from here on we shall simply use the term rulemaking to refer to the informal variety.

Guidance Development

Similarly, guidance development comes in two flavors—level 1 and level 2 guidance documents. The difference between the two is that level 1 guidance requires an opportunity for public comment *before* implementation, and level 2 does not. Level 1 is reserved for guidance that plows new ground, addresses controversial topics, makes significant policy changes or tackles complex science. Level 2 is used for all other guidance. FDA conducts guidance development using its website, and only employs the *Federal Register* to announcement level 1 guidance.

Public Outreach and the Sunshine Laws

So, for both rulemaking and guidance development, the public—including industry—has the right to comment on proposed Agency policy. But most people would agree that simply commenting on a fully developed policy option is not always the best and most efficient way to arrive at the optimal public policy. Earlier dialogue among the Agency and the various stakeholders is more likely to lead to the best policy, quickly.

That's where the sunshine laws start to apply. One of those laws, the Federal Advisory Committee Act (FACA), governs how federal agencies obtain advice from groups of private citizens. Whenever an Agency considers meeting with outside stakeholders, it must think through whether the meeting is, in effect, an advisory committee meeting. And the answer is not always intuitively obvious.

Specific Requirements

In the following sections, we will discuss the primary laws that require public involvement in rulemaking and guidance development, as well as the sunshine laws that need to be navigated in achieving that public involvement. In addition to describing what a law requires, we'll discuss whatever restrictions the law might specifically place on people—from industry or other stakeholders—helping the Agency.

1. Meetings

Federal agencies, such as FDA, often meet with stakeholders. In most instances, one-on-one meetings with stakeholders do not present any legal issues. However, if the meetings start to look more like committee meetings, FACA might apply. Furthermore, FACA might apply whether the purpose of the meeting is to discuss a rule, guidance, or any other policy matter.

1.1. Purpose of the laws

FACA was designed to counter the undue influence of special interests by ensuring that the membership of federal advisory committees is balanced and that the committee meetings and minutes are open to the public. The Act also controls the number and cost of these committees. When Congress passed the legislation, Congress found that there were "too many inactive, meaningless, obsolete and redundant committees," and, at the same time, that other "committees were so powerful that they, in effect, constituted a fifth arm of government."[40]

1.2. What the law requires

FACA requires that federal advisory committees:

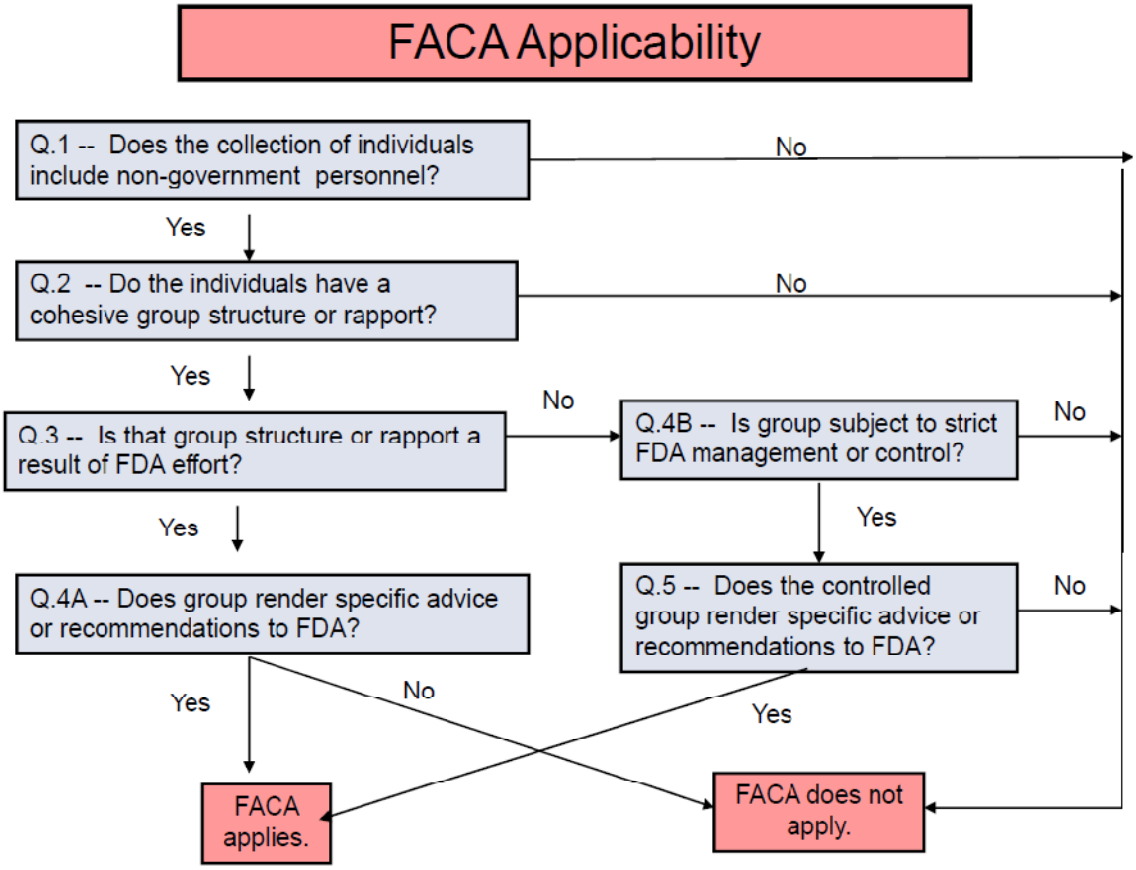
- ✓ Establish a written charter that explains the mission of the committee,
- ✓ Give timely notice of meetings in the *Federal Register*,
- ✓ Have fair and balanced membership,
- ✓ Open meetings to the public whenever possible,
- ✓ Have the sponsoring Agency prepare minutes of meetings,
- ✓ Provide public access to the information used by the committee,
- ✓ Grant to the federal government the authority to convene and adjourn meetings, and
- ✓ Terminate within two years unless the committee charter is renewed or otherwise authorized by statute.

1.3. Relevant Restrictions

[40] 5 U.S.C. App. 2, § 2 (2006).

As you can tell from that list of requirements, complying with FACA can be very burdensome. Furthermore, certain Executive Orders have placed limits on the number of FACA committees an Agency may use. So ordinarily, agencies try mightily to avoid conducting meetings that would trigger FACA.

What is that trigger? Unfortunately, as with many laws, drawing the line that defines what activities are regulated is very complicated and not always clear. The best way to understand it is to use the following chart:



The questions on the chart seem deceptively simple, but many of them are very complex and require weighing various factors.

Question 1, for our purposes, will always be answered "yes" because we are trying to figure out ways through which industry can work together with FDA.

Question 2 concerns the capacity in which the individuals involved are acting. Are they each simply speaking for themselves, or are they working together to identify a consensus position? If the individuals are simply speaking for themselves, FACA does not apply. To answer this question, FDA may consider whether the individuals and the meetings are characterized by:

- ✓ A fixed membership,
- ✓ A formal organizational structure,
- ✓ Regular meetings,

- ✓ A fixed agenda, and
- ✓ Above all, a specific, defined purpose.

There is no formula for weighing those factors, only guidance from courts suggesting that the last factor is perhaps the most important.

Question 3 speaks to the initial organization of the group: does the group exist in the first place thanks to FDA, or did it have its own, independent existence prior to any contact with the Agency?

If the group owes its existence to FDA, we move to **question 4A,** which concerns how the group functions. If the group supplies advice to the Agency on some specific policy issue or proposal, FACA applies. If instead the group simply offers FDA general commentary, suggestions, or raw data, FACA does not apply.

We turn to **question 4B** if the group does not owe its existence to FDA. In that instance, we ask whether the group is "controlled" by the Agency. Determining whether FDA controls the group requires examining a variety of factors, including whether:

- ✓ FDA appoints the members to the group,
- ✓ The group receives Agency funding,
- ✓ FDA sets the group's agenda, and
- ✓ The group answers directly to the Agency.

If the group is controlled by FDA, in **question 5**, as in question 4a, we ask whether the group supplies advice to the Agency on some specific policy issue or proposal.

If that seems complicated, it is. And frankly, that is why agencies such as FDA worry so much about it. Years ago, FDA and other agencies were sued quite often over FACA violations and, in some cases, lost. More recently, though, agencies have generally been victorious, but that may also reflect greater caution by agencies regarding how they work with members of the regulated community.

The best way to truly understand FACA is to go through some case studies, as we do below.

1.4. References

1.4.1. Federal Advisory Committee Act, 5 U.S.C. App. 2 (2006), enacted Oct. 6, 1972, Pub. L. No. 92-463, 86 Stat. 770.

1.4.2. General Services Administration, Federal Advisory Committee Management Regulations, 41 C.F.R. Part 102-3.

1.4.3. 21 C.F.R. § 10.65 on meetings

1.4.4. Croley, S., "Practical Guidance on the Applicability of the Federal Advisory Committee Act," 10 Admin.L.J., 111-178 (1996).

2. Guidance Development

2.1. Purpose

In many instances, rather than create an enforceable rule, FDA merely wishes to communicate with the regulated community the Agency's expectations in complex and technical areas. To do so, rather than going through the elaborate rulemaking process, the Agency issues less formal

guidance. FDA developed its GGPs to ensure that the guidance development process was open and transparent, efficient, and well-organized.

2.2. What the law requires

Although FDA had already developed informal GGPs, Congress decided to codify the guidance development process requirements in the Food and Drug Administration Modernization Act of 1997. In that legislation, Congress specified that FDA develop guidance documents with public participation. FDA then elaborated on that statutory amendment by adopting GGP regulations.

The final regulations, as well as the history of GGPs at the Agency, make it abundantly clear that FDA wanted to encourage meetings and other such casual forms of communication as a part of the guidance development process. Two highlights of the regulatory history illustrate that point:

1. The original GGPs adopted by the Agency before the 1997 legislation explicitly stated the Agency's objective of ensuring that public participation can occur at the earliest stages of the process.[41] In the *Federal Register* notice announcing the procedures, the Agency explained:

> Because the agency recognizes that it is important to solicit input prior to its decision to issue a guidance and also, perhaps, during the development of a draft of a Level 1 guidance, the agency is implementing various practices to obtain input at the earliest stages of Level 1 guidance document development.[42]

Elsewhere in the notice FDA specifies some of the ways that input can be obtained:

> FDA may solicit or accept early input on the need for new or revised guidance or assistance on the development of particular guidance documents from individual nongovernmental groups such as consumer groups, trade associations, patient groups, and public interest groups. . . . The agency may also hold meetings and workshops to obtain input from each interested party on the development or revision of guidance documents in a particular FDA subject area.[43]

2. The final regulations promulgated in September 2000 reiterated the importance of the Agency meeting with stakeholders prior to and during the development of guidance documents. In language very similar to the earlier notice, FDA observed that "early collaboration . . . can be a very valuable tool in developing

[41] The Food and Drug Administration's Development, Issuance, and Use of Guidance Documents, 62 Fed. Reg. 8961 (Feb. 27, 1997), *available at* http://www.gpo.gov/fdsys/pkg/FR-1997-02-27/pdf/97-4852.pdf.

[42] *Id.* at 8968.

[43] *Id.*

> regulatory guidance. . . . [To that end, the agency] may hold meetings or workshops even before the agency develops a draft document."[44]

Thus, on both occasions when FDA put into writing its GGPs, the Agency embraced the concept advocated in many comments that the Agency be open to various forms of communication both before and during guidance development.

2.3. Relevant Restrictions

In a nutshell, other than the general prohibitions against the improper use of advisory committees and other general limitations on how an Agency interacts with the regulated community (e.g., prohibiting bribery), there are no legal restrictions on communication that can occur before or during guidance development. And intuitively, why should there be? Guidance documents, unlike regulations, are not legally binding. There simply is no reason why the Agency should be restricted legally in its communications.

That said, FDA may very well have other, non-legal reasons to avoid appearing too close to any particular group as the Agency develops guidance documents. Given the highly visible and often controversial role the Agency must play, these governmental reasons must be respected. Further, matters of administrative efficiency also mean that FDA can't meet with whoever wants to meet whenever they want to meet. But those factors should not be confused with a legal limitation on communication.

2.4. References

2.4.1. Section 405 of the Food and Drug Administration Modernization Act of 1997, amending section 701(h) of the Federal Food, Drug and Cosmetic Act, found at 21 U.S.C. § 371(h).

2.4.2. 21 C.F.R. § 10.115 on Good Guidance Practices

3. Rulemaking process

3.1. Purpose

The Administrative Procedures Act (APA), which sets forth the basic requirements for conducting rulemaking by any federal Agency, is designed to ensure that the rules agencies produce are well supported by a factual record and are unbiased by special interests. In soliciting input from the public, the law seeks both to bolster that factual record and to ensure fairness. The public, particularly the portion of the public on whom the compliance obligations will fall, also is more likely to support a rule for which it had the opportunity to provide input.

3.2. What the law requires

Notice and comment rulemaking requires that an Agency develop a proposed rule, publish that proposed rule in the *Federal Register*, solicit public comment during a defined period of time, and ultimately issue a final rule that includes an adequate statement of the rule's basis and

[44] Administrative Practices and Procedures; Good Guidance Practices, 65 Fed. Reg. 56,468, 56,470 (Sept. 19, 2000), *available at* http://www.gpo.gov/fdsys/pkg/FR-2000-09-19/pdf/00-23887.pdf. *See also* 21 C.F.R. § 10.115(g)(i).

purpose. That statement of basis and purpose becomes the administrative record that a court would review if asked to judge the rule's legality.

3.3. Relevant Restrictions

Contrary to popular opinion, the APA does not prohibit contact between members of the public and the Agency concerning a rule under development through notice and comment rulemaking. Some of the confusion stems from the fact that the other form of rulemaking—formal rulemaking that employs a trial-type public hearing—does prohibit certain forms of contact. But notice and comment (a.k.a. informal) rulemaking includes no such restriction.

Nonetheless, in the past, a few courts have found bias in a rulemaking when there is too much one-on-one contact between certain members of the public and the Agency officials developing a proposed rule. In those cases, they have invalidated the rule on the grounds that it is based on evidence not in the administrative record (the official file at the Agency in which the comments are kept). The solution to that problem, then, is for the Agency to make sure that the substance of conversations about a proposed rule ends up in the record. And that is precisely what FDA regulations require.

- ✓ Section 10.40 lays out the procedures for rulemaking, and specifically explains in subsection (f)(1) that in addition to obtaining formal written comments, the Agency may subject a proposed or final rule, before or after publication in the *Federal Register*, to additional conferences, meetings, discussions and correspondence under section 10.65.
- ✓ Section 10.65 in turn covers general meetings and correspondence, and simply notes that the Agency may meet with interested parties, including private meetings with members of the public. That section further specifies that FDA should prepare a memo summarizing the meeting and should file that memo in the appropriate administrative record.

Furthermore, most legal experts agree that the rules are even less restrictive when the conversation in question occurs before a proposed rule is even published.

Those are the rules with regard to what a private citizen might tell FDA. With regard to what FDA might tell private citizens, the Agency is not permitted to tell people what is going to be in a proposed rule before it comes out for the simple reason that such communication would give some parties an advantage over others. The comment period is always defined in the notice that accompanies the proposed rule, and telling some people early about the content would give those people longer to formulate their comments. That isn't fair.

Those are the legal obligations for rulemaking. Of course FACA requirements must be read on top of the APA requirements. Further, as with guidance development, the public must understand that for good government reasons the Agency needs to avoid the appearance of any special access on the part of any individual members of the public. But, bottom line, the law does not prohibit conversations with the Agency concerning proposed rules.

3.4. References

3.4.1. 5 U.S.C. § 553, for informal rulemaking under the Administrative Procedures Act.
3.4.2. 21 C.F.R. § 10.40 for FDA's informal rulemaking process.
3.4.3. 21 C.F.R. § 10.65 for FDA meetings
3.4.4. Croley article, supra, for FACA explanations.

Ways to communicate

Based on those laws, some possible avenues for collaboration with FDA before and during rulemaking and guidance development include:

1. Public meetings, including FDA workshops, conferences etc. (§ 10.65(b));
2. Private meetings with specific industry groups on FDA's premises where summaries are filed with the comments (§10.65(d));
3. Industry hosted meetings that FDA attends (like a trade association's annual meeting) (§ 10.65(e));
4. Standards activities organized by appropriate standards development organizations (for example, AAMI) (§ 10.95);
5. Capitol Hill-convened meetings;
6. Meetings convened by a neutral third party (*e.g.*, FDLI);
7. Written communication, either e-mail or other correspondence (§10.65(f));
8. Discussion as part of an advisory committee meeting.

Some communication technologies to use, which are governed by the same rules as face-to-face meetings, include:

1. Telephone conference calls
2. Video desktop conferencing
3. Electronic chat rooms
4. Internet broadcasts of various types

Examples

The best way to understand these various rules is to consider a few case studies. Below for each case study we will present a hypothetical scenario, and then analyze it.

Case Study One.

Suppose FDA decided to hold a town meeting to provide a one-time forum for any interested party to voice its opinions and concerns to the Agency on the topic of the appropriate design of a clinical trial to support a premarket approval application. Imagine that the time and place of the meeting were determined in advance, and that the costs of the meeting—the rental price of the meeting place, for example—were paid by the Agency. Finally suppose that the FDA publicized its meeting in advance on its website, inviting any parties interested in participating to attend.

Quite clearly, this conduct would not trigger FACA. The Agency obviously did not utilize an existing group for advice or recommendations. Nor did FDA in the scenario establish the group. The town meeting took place only once, involved a group of participants not designated by the Agency—indeed not identifiable before the event—and otherwise exhibited no organizational structure. In addition, simply by holding the meeting the Agency did not solicit the collective views, as opposed to the individual views, of those who attended.

Case Study Two

Imagine FDA sought to gather the individual views of several recognized experts on the proper design of clinical trials. FDA determined that it was most convenient to hold one long meeting on a single day and have all these experts meet with the Agency personnel at once. At this one-time meeting, FDA personnel questioned the experts, one at a time. Each expert, in turn, explained to the Agency her position regarding the clinical trial question. FDA personnel kept careful notes of each expert's view. After the last expert addressed the Agency, the meeting was adjourned, with no time reserved for a general discussion session among the experts.

Under these circumstances as well, the Agency's conduct would not trigger FACA. The mere fact that the Agency assembled the experts at once does not affect FACA's applicability where, as explained here, the experts in no way interact or otherwise function as a unit or a group.

Case Study Three.

Imagine FDA sought Device Trade Group's recommendation about whether the Agency should promulgate a new rule concerning the proper design of clinical trials for premarket approval. To get Device Trade Group's advice, the Agency convened a series of meetings attended by the Agency's own personnel as well as Device Trade Group staff. No other medical device group or consumer group was invited to the meetings, nor were individual company representatives invited. Further, while the Agency's primary purpose in hosting the meeting was to get the group's advice on clinical trials, FDA and Device Trade Group staff also happen to discuss the merits of the Agency's policy on some closely related issues involving premarket approval.

FACA would not apply to the Agency's conduct in these circumstances either. Although FDA solicited specific advice respecting a particular policy issue identified, and although the Agency solicited that advice through scheduled meetings, the advice came from an independent, pre-existing group, not established by the Agency. Put differently, the important question would be whether FDA so tightly controlled Device Trade Group that it utilized Device Trade Group for the purpose of obtaining advice. But on the facts provided, the Agency exercised no control over Device Trade Group, much less tight control. FDA invited the group to the meetings, and Device Trade Group came, but in no way did the Agency shape Device Trade Group's composition, management, perspective, deliberations, or agenda.

Case Study Four.

As in the first case study involving the town meeting, suppose now that the Agency's meeting was so successful that FDA decides to institutionalize the event, and conduct it every few months somewhere within the same geographical area. Over time, the number of attendees stabilizes to a group of 15 loyal regulars, who develop a sense of group rapport, seeing themselves as a cohort interested in the same set of issues. As a result, FDA decides to use the group, repeatedly, as a sounding board for specific proposals the Agency is in the process of developing. Knowing who will attend the meeting, given that the group of participants has stabilized, before each meeting FDA sends out an agenda it plans to cover the next time the parties convene. At each meeting,

those who attend are given a chance to address FDA about their own concerns, but time is always reserved for the Agency to explain its agenda and to tap the views of those in attendance. Still, however, the group lacks formal organizational structure; it has no chair, no secretary, and no minutes are kept at the meetings.

Under these facts, FACA may apply. Although the group has no formal structure, its membership is stable. Furthermore, the subject of discussion is prepared in advance of the meetings, and addresses topics which FDA itself identifies. Moreover, those topics include specific proposals under consideration at the Agency.

Case Study Five

Consider again the second case study involving a meeting of experts. Suppose that instead of seeking experts' individual views, FDA sought the collective view. However, the Agency still scheduled only one meeting, for the limited purpose of giving experts an opportunity to present their collective view on clinical trials. The meeting did not, in other words, provide the experts with an opportunity to discuss the regulatory issue in question. Instead, FDA had instructed the experts to meet on their own time, at their own initiative and without Agency involvement. So FDA's meeting with the experts took place after the experts had themselves already met. At the FDA meeting, the experts presented the Agency with a sharply divided report containing the experts' majority and minority views on the issue under the Agency's consideration.

FACA may apply. Although no FDA personnel participated in the experts' prior meetings, and although those meetings produced no consensus view, still the Agency under these facts established a group composed of non-employees with the specific intent of obtaining advice on a particular question. The group of experts, who had no organization prior to their enlistment by FDA, met, deliberated, and subsequently communicated their collective although divided advice to the Agency, all at the Agency's instigation.

Case Study Six.

Return to the example of where FDA invited Device Trade Group (Case Study Three). Now suppose that the Agency, seeking the advice of the drug and medical device communities generally, created an entirely new group composed of representatives from leading trade associations. Suppose also that FDA scheduled a series of meetings for the new group's members to discuss whether the Agency should promulgate a new rule to prescribe the proper design of a clinical trial, with the intention of relying on the group's advice. Finally, suppose that FDA designated the representative of one of the trade groups to serve as the group's Secretary, and another to be its spokesman.

FACA would apply. Indeed, FDA's conduct now satisfies every item on the checklist of criteria for triggering the Act. The Agency established the group, appointed all of its members, gave it an organizational structure, and directed it to consider a substantive policy issue and to advise the Agency about whether to respond to that issue. Although FDA could have solicited advice from individual group members speaking on behalf of their respective trade associations without "utilizing" those groups, the Agency instead decided to establish a group.

Frequently Asked Questions

1. General Meetings

   Q.1. May my company meet with FDA to discuss a policy issue that concerns us?

   A. Yes, a single company meeting with FDA will not trigger a FACA concern, and FDA may legally meet even to hear the company's concerns regarding a topic of rulemaking. In the latter case, the Agency should memorialize the subject of the meeting for the rulemaking file.

   Q.2. _____

2. Guidance

   Q.1. May I talk with the Agency after they have announced plans to develop a guidance document but before they have published the proposed guidance, on the subject of the guidance?

   A. Yes. Of course the rules regarding FACA need to be observed. But there is simply no other legal impediment to these discussions.

   Q.2. May I talk with the Agency after they have published a proposed guidance but before they have published the final guidance, on the subject of the guidance?

   A. Yes. Again, FACA needs to be observed. And in this case, FDA might find it good practice to summarize the conversation and put that summary in the comment file for the proposed guidance.

   Q.3. _____

3. Rulemaking

   Q.1. May I talk with the Agency after they have announced plans to make a rule but before they have published the proposed rule, on the subject of the rule?

   A. Yes. As before, the rules regarding FACA need to be observed. But there is simply no other legal impediment to these discussions.

   Q.2. May I talk with the Agency after they have published a proposed rule but before they have published the final rule, on the subject of the rule?

   A. Yes. Again, FACA needs to be observed. In this case, FDA should summarize the conversation and put that summary in the comment file for the proposed rule.

   Q.3. Prior to rulemaking, may I ask FDA what its proposed rule will say?

   A. No, because fairness dictates that all members of the public have an equal opportunity to comment. If the Agency answered your question, it would be giving you longer to comment.