October 14, 2010

VIA ELECTRONIC SUBMISSION

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

Re: Comments on Medical Device User Fee Act; Docket No. FDA-2010-N-0389

Dear Sir or Madam:

The Combination Products Coalition ("CPC") is pleased to offer its comments in response to the August 13, 2010, *Federal Register* notice regarding the reauthorization of the medical device user fee program. User fees are an important part of supporting Agency activities not only on marketing submissions, but also with respect to policy-making and guidance document development. We believe that the next iteration of the medical device user fee program should have more focus on CDRH's ever-critical policy-making activities, including with respect to CDRH's participation in guidance document development for combination products.

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 area. One of the principal goals of our organization is to work 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.

The *Federal Register* Notice requested comments on what aspects of the medical device user fee program should be retained, changed, or discontinued to further strengthen and improve the program. Our comments focus on the importance of the Agency's development of guidance documents, and in particular, two aspects of the program that the Agency should enhance and one aspect of the program that the Agency should retain.

By way of background, on August 7, 2009, the CPC submitted extensive comments on the Agency's transparency initiative and the way in which the Agency should improve transparency in its processes and decision-making by increasing focus on its guidance document development. A copy of these comments is included at Attachment A.

1. Make guidance development a higher priority.

Regulated industry generally, and the combination products industry in particular, needs guidance on a number of issues. Due to the diverse nature of combination products, this need impacts the Office of Combination Products, as well as multiple Centers. As far CDRH's role, the medical device user fee program should recognize the integral role CDRH plays with respect to combination product guidance development, particularly those guidance documents that address issues pertaining to medical devices as constituent parts of a combination product.

The current medical device user fee commitment letter essentially states that the agency will develop guidance when it has time, given the priority of marketing submissions. As currently stated, this commitment does not adequately recognize the importance of guidance document development. A critical part of agency transparency and efficiency is developing guidance that explains the agency's views in important areas. Guidance also helps preserve agency resources by disseminating information to a broad public audience, rather than requiring the agency to respond to numerous individual requests for information (for example, FOIA requests) and by establishing a consensus on how to meet requirements, thereby potentially reducing the number of meetings with industry on specific applications. In this regard, guidance development, particularly on pre-submission issues, should help improve the quality of marketing submissions, thus streamlining the agency's clearance and approval processes.

In summary, any new user fee commitment letter should reflect a firm commitment to guidance document development, including CDRH's active and timely participation in the development of any relevant combination product guidance.

2. Use the published list of guidance documents under development as a tool for dialogue between the Agency and stakeholders on guidance development priorities.

As part of Good Guidance Practices ("GGPs"), the Agency publishes an annual guidance document agenda of possible guidance topics or documents for development or revision during the coming year.[1] This list allows stakeholders to understand and begin thinking about the Agency's planned guidance topics. The public can comment on Agency priorities, topics for consideration, and similar issues.

However, the annual guidance development plan has not been as helpful as it could or should be. In particular, typically the Agency does not offer feedback to the public or regulated industry on their comments on the list and, to our knowledge, does not revise the list to reflect

[1] 21 CFR § 10.115(f)(5).

comments received. We are concerned that FDA considers this list merely a chore, and thus does not embrace the process to ensure the list has real meaning.

To ensure the list is a useful communication and planning tool, the Agency should go beyond the bare minimum required by GGPs and should use the list to engage with the public on guidance document development priorities. An interactive dialogue would serve the dual benefit of focusing the Agency on areas in which guidance is most needed and enabling the public and regulated industry to understand better the Agency's perspective on the challenges and ambiguities seen by the Agency. Such a dialogue should result in more useful guidance for all Agency and industry stakeholders, and thus better serving the public health. The user fee commitment letter should reflect this enhancement.

3. <u>Preserve informal communications and dialogue between the Agency and stakeholders.</u>

Gaining input on an informal basis is vitally important to regulated industry and helps the agency's workflow by making market submissions and post-market compliance more efficient. Such informal communications include inter-Agency consultations between and among the Office of Combination Products and the various agency Centers, consultations between regulated industry and the Agency, and dialogue between the Agency and the public through workshops or public meetings. These types of communications are not tracked in any formal metric for user fee purposes; however, they are critically important and should remain a co-equal priority with other agency activities. In this regard, the Agency should ensure these informal types of communications are preserved and not diminished by the user fee program's usual focus on more formal and quantitatively-measured interactions.

* * *

User fees offer critical support to a variety of agency activities, including guidance document development. Because guidance on agency policy is as important as ever before, the reauthorized medical device user fee program should reflect and support this importance.

Respectfully submitted,

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On behalf of the Combination Products Coalition

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APPENDIX A:

Combination Products Coalition

Comments on Agency Transparency

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August 7, 2009

VIA ELECTRONIC SUBMISSION

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

Re: Docket No. FDA-2009-N-0247; Food and Drug Administration Transparency Task Force; Notice of Public Meeting; Request for Comments

Dear Sir or Madam:

On behalf of the Combination Products Coalition ("CPC"), we welcome the opportunity to offer comments on ways in which the U.S. Food & Drug Administration ("FDA") can make information about agency activities and decision-making more accessible to the public. Ensuring appropriate transparency and providing accessible and easy-to-understand information are important goals that the CPC wholeheartedly supports.

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 special, broad and unique perspective to the questions surrounding FDA's transparency.

Indeed, over the past year (well before the agency announced this initiative), we consulted with numerous companies, other trade associations, fellow food & drug counsel and people from the agency in an effort to better understand the collective public's need for transparency and practical solutions to those needs. To that end, you will find examples in this letter from other industries such as the food industry. We also drew on the undersigned's long-standing interest in the agency's guidance development process. In the mid 1990s, the undersigned filed and advocated over a period of years the Indiana Medical Device Manufacture's Council petition that led FDA to adopt the Good Guidance Practices ("GGPs").

That movement broadened over the years and also led to statutory changes. We have been monitoring the agency's progress ever since.

We are very pleased the agency has undertaken this initiative, and below we offer our recommendations on ways to improve the agency's transparency in its processes and decisions.

EXECUTIVE SUMMARY

For an agency like FDA, two basic administrative functions should be transparent: (1) rule and policy-making and (2) individual decision-making and adjudication. At a high level, rule-making under the Administrative Procedure Act and guidance development create transparency for the broad decision-making, whereas The Freedom of Information Act ("FOIA") and other such law create transparency with respect to individual adjudication.

As we examine how the agency should ensure appropriate transparency in policy-making, much of our thinking centers upon guidance issued by the agency – both the process used for issuing guidance, as well as the ultimate guidance document. Really this isn't surprising, as guidance is the agency's primary vehicle for communicating regulatory process and substantive expectations to the public and industry. Quite simply, good guidance creates transparency. Through the implementation of GGPs more than 10 years ago, the agency made vast improvements in both guidance content and process. However, we think now is the right time to examine the current state of GGPs and refocus the agency's continued application of these principles. It's time for GGP 2.0.

In general, we suggest the agency improve transparency in its policy-making by:

1. **Embracing** the idea that the agency can freely communicate with the public before and during the guidance development process outside the formal notice and comment mechanism.
2. **Producing** more guidance. There are many critical areas where guidance is needed to clarify the agency's expectations.
3. **Adopting** procedures designed to ensure that the content of guidance addresses the public's key questions.
4. **Responding** to comments. It's the only way we can really know why the agency makes the decisions it makes and thus what the agency expects.
5. **Finalizing** draft guidance. The agency has developed a habit of leaving guidance in draft interminably. The agency should also work to finalize or come to closure about proposed rules with a set timeframe.
6. **Employing** metrics designed to track the agency's progress in guidance development.
7. **Continuing** to avoid using speeches, warning letters and other such communications to announce new policy that should be in guidance.
8. **Investing** more time in planning guidance development. We hope the agency will be more proactive in planning the topics to address in guidance, and will follow its plan.

With regard to improving transparency in individual decision-making and adjudication, we ask FDA to:

1. **Preserve** access to carefully chosen regulatory information—as distinct from company information—while maintaining the rights of information owners under the administrative and trade secret laws.

In support of transparency in both broad decision-making and individual adjudication, we ask that FDA:

1. **Participate** in joint training that promotes a common understanding of inspection and enforcement processes.
2. **Clarify** the roles and responsibilities of various agency offices to allow easier public access to information.

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I. TRANSPARENCY IN POLICY-MAKING

a. The agency's implementation of Good Guidance Practices in the 1990s dramatically improved transparency.

After the GGPs were originally introduced in response to the Indiana Medical Device Manufacturers Council petition, the agency made tremendous improvements in guidance development. Here's just a sampling of these improvements:

BEFORE GGPS	AFTER GGPS
Guidance lacking in detail and comprehensiveness	Consistently higher quality guidance
Outdated drafts	Avoided superseded drafts
No clear agency sign off/support	Clarified agency sign off and support and improved developing cross-center guidance
Hard to find	Much easier to find on the agency's website
Frequently used speeches to announce new policy	Fewer instances of "podium policy"
Implemented while in draft form	Guidance clearly marked with regard to draft status (though sometimes still applied in this form)
Applied as rules	Guidance clearly phrased as non-binding recommendations
Often not responsive to the public's needs for clarity	Sometimes more responsive to the public's need for clarity; for example, publishing the annual guidance development plan

In all, the agency has made significant and laudable improvements in developing guidance.

b. The time is right for GGP 2.0.

Notwithstanding those tremendous strides forward, we think the agency can greatly enhance transparency in its policy-making by refocusing its attention on certain fundamental principles surrounding the GGPs. We are not suggesting the need for any changes to the statute or regulations: the agency just needs to invest more effort where implementation has become lax and make a few improvements in certain areas. As we like to say, the agency should undertake GGP 2.0.

In the context of guidance, transparency has two elements:

- Content – The content of the guidance document usually communicates and makes transparent what FDA expects of industry in the way of compliance or how FDA plans to conduct an administrative process.

- Process – The guidance development process plays a pivotal role in FDA's regulatory schemas, and that development process itself needs to be transparent.

Below we describe our views of what GGP 2.0 should entail in order to improve both guidance content and the process.

1. *Embrace informal communication during guidance development.*

Given that our objective is to increase transparency, FDA should not use GGPs as a shield or as a reason why the agency cannot engage in dialogue while the agency is thinking about guidance. In recent years, we have encountered instances in which FDA staff members mistakenly believe the law somehow prevents communication while guidance is being considered. However, neither the APA, nor any other federal law precludes such interaction merely because FDA is planning to issue guidance. Gaining input on policy topics, for example through workshops or public meetings, is vital to the agency's regulatory mission, and it should not be shut off by a misinterpretation of administrative law.

The confusion may have started when people at the agency compared guidance development to rulemaking and the rules on *ex parte* contact in rulemaking. However, the APA does not prohibit contact between members of the public and the agency concerning a rule under development through notice and comment rulemaking, also known as informal rulemaking.[1] While the other form of rulemaking—formal rulemaking that employs a trial-type public hearing—does prohibit certain forms of contact, notice and comment rulemaking employs a different process.

To be sure, 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, courts have invalidated the rule on the grounds that it is based on evidence not in the administrative record. But the solution to that problem is for the agency to make sure that the substance of public meetings and conversations about a proposed rule ends up in the record, which happens to be what FDA regulations require.[2]

Moreover, the GGP regulations, as well as the history of GGPs, make it clear that the agency 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] 5 USC § 553.
[2] 21 CFR § 10.40(g).

First, the original GGPs adopted by the agency explicitly stated the agency's objective of ensuring that public participation can occur at the earliest stages of the process.[3] 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.[4]

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.[5]

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, the agency observed that "early collaboration can be a very valuable tool in developing regulatory guidance. To that end, the agency may hold meetings or workshops even before the agency develops a draft document."[6]

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

Further, other than 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.[7] The agency and the public need to figure out how to communicate comfortably in guidance development.

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[3] 62 Fed. Reg. 8961, *The Food and Drug Administration's Development, Issuance, and Use of Guidance Documents* (Feb. 27, 1997).
[4] *Id*. at 8968.
[5] *Id*. at 8965.
[6] 65 Fed. Reg. 56,468, *Administrative Practices and Procedures; Good Guidance Practices* (Sept. 19, 2000); *See also* 21 CFR § 10.115(g)(i).
[7] Of course, FDA may 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,

In particular, in the course of guidance development, FDA also should reach out more deliberately and extensively to patient and consumer groups to solicit their viewpoints. Many consumer groups are not well funded and do not have the personnel to track and react to policy development in the same way that some within industry might. Moreover, because many consumer and patient groups are also less likely to have representation in the Washington/Maryland area, FDA should use means and media that can help overcome geographical limitations.

2. *More guidance is needed.*

We have also noticed that the production of new, important guidance documents has slowed dramatically. Again, a critical part of transparency is developing guidance that explains the agency's views in important areas. Guidance also helps preserve agency resources by disseminating information to a broad public audience, rather than requiring the agency to respond to numerous individual requests for information (for example, FOIA requests). In all, FDA simply is not making full use of guidance. Consider the following examples.

- Companion Technologies Development – Companion technology development involves developing a diagnostic test that is administered in order to determine whether a specific drug should be prescribed or whether the result of a diagnostic test can/should be used to guide a treatment decision, such as drug selection or dosing. The current regulatory framework for companion technologies is neither transparent nor consistent, and an FDA guidance document is needed. While FDA released a Concept Paper in 2005, that paper has never advanced to a formal draft guidance.[8] Companion technology development involves multiple agency Centers and the Office of Combination Products, and coordination among them is part of the challenge in developing a guidance document.

- Internet Promotion – In March 2009, FDA sent a series of untitled letters to drug manufacturers warning that the companies' search advertisements — the short text ads that run beside Google results — had to start including risk information about each drug or else be rewritten or removed.[9] In the absence of FDA guidance on internet promotion, manufacturers and advertisers assumed that a "one click" rule was permissible – i.e., as long as the companies provided risk information within one click of their search ads, then they would be compliant. FDA could have easily cleared up the policy in this area through guidance. Rather, FDA issued untitled letters that have led to continued confusion about FDA policy regarding internet promotion.

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these governmental reasons must be respected. Further, matters of administrative efficiency also mean that FDA can't meet with whomever wants to meet whenever they want to meet. But those factors should not be confused with a legal limitation on communication.

[8] FDA has again requested feedback on the old concept paper to reflect updated issues. The agency has also suggested that it may release a series of white papers on the rapidly developing concept, and has solicited ideas for such a white paper series.

[9] A list of these letters is available on FDA's website, at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/UCM055773 (last accessed July 21, 2009).

- Risk Evaluation and Mitigation Strategies (REMS) – Congress created the statutory concept of REMS in September 2007 as part of FDAAA, and the new authority became effective in March 2008.[10] In the year and a half since, industry and FDA alike have struggled to understand the REMS requirements and to reconcile REMS with the previous RiskMAP process. Industry has been left to interpret FDA's REMS policy from action letters and approval documents while FDA works to develop guidance on REMS and the REMS assessment process. The guidance was originally expected in fall 2008, but it has still not been issued. It is understandable that FDA must gain adequate experience with reviewing and assessing REMS before issuing guidance, but we believe that the unwieldy guidance development and clearance process has led to delays in issuing the draft guidance. This has contributed to significant uncertainty among regulated industry and the larger healthcare delivery system, on a very important topic.

- Adaptive Trial Design – Under PDUFA IV, FDA committed to issuing draft guidance on adaptive clinical trial design by the end of Fiscal Year 2008,[11] but issuance of the guidance has been delayed, due in part to the scientific complexity of the topic, as well as the burdens of the clearance process. This is an important scientific area under the Critical Path initiative and a significant tool for studying subpopulation effects in the most efficient and effective manner. In the absence of an FDA guidance, sponsors may be hesitant to apply the principles of adaptive trial design, thereby slowing the advancement towards personalized medicine.

- Food and Nanotechnology – As with other industry sectors, the food industry is also struggling with how to handle nanotechnology as applied to food. Although the agency has held workshops on food/nanotechnology issues, we understand that guidance may not be issued until 2010.

- Combination Products – In late 2007, the member companies of the Combination Products Coalition ("CPC") developed and sponsored an online survey designed to gauge industry priorities for guidance and rulemaking activities in the realm of combination products. The survey results were clear that industry would like additional guidance—and in more detail—on combination product issues. As informed by both the survey and our discussions with stakeholders, the top priorities with respect to specific combination product guidance documents would be:

    1. Good Manufacturing Practices ("GMPs") applicable to combination products;[12]

[10] 21 USC § 355-1.

[11] FDA, PDUFA IV Reathorization Performance Goals and Procedures; Fiscal Years 2008 through 2012, available at: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm119243.htm (last accessed July 21, 2009).

[12] The Agency announced its intent to propose regulations for GMPs for combination products in the spring of 2006. Prior to that, the Agency had promulgated a draft guidance document on applying GMPs to combination products in September 2004. Although this guidance has been helpful, the combination products industry needs additional guidance on the application of the GMP regulations.

2. Clinical trials on combination products; and
3. Post-approval product modification issues.

To date, the agency has not issued guidance on these topics.

To rectify these declines in guidance development, we think the first step is to identify the root cause of the problem. We on the outside of the agency can only speculate as to that root cause, but possibilities include:

- The mechanics of the guidance development process have gotten so complex that the burden now outweighs the benefit to the agency. It's just easier for the agency to use speeches, warning letters, and draft guidance (see below).
- The agency simply lacks appropriated resources to do the job.
- The guidance development function is not appropriately prioritized, in part because industry user fees generally are not applied towards product or disease-specific guidance.
- There is a lack of alignment between public stakeholders and the agency as to what guidance is important, and the agency does not pursue the guidance the public thinks is most important.
- The agency prefers strategically not to be proactive, letting regulatory issues play out without committing to specific guidance.

We recommend that the agency convene a public meeting to explore these possible root causes and the appropriate remedies. Guidance is too important to be hindered by these factors.

3. ***Produce helpful guidance, responsive to industry's needs.***

To be honest, the guidance FDA produces is not always useful. By this, we don't mean we disagree with the content, but rather the content sometimes doesn't answer the key questions that the public has. We believe that a central reason for this is FDA does not spend enough time up front soliciting from the public the key questions that need to be answered. By skipping this step, the Agency ends up writing a guidance document that only addresses the agency's theoretical concerns and enforcement issues, rather than the need of the public for clarity and transparency.

- Good Importer Practices – This draft guidance recognizes that it applies to all FDA-regulated industries – from drugs and biologics to food and cosmetics.[13] Consequently, it does not provide a level of detail to individual industry sectors sufficient to achieve the goals of the guidance. As the guidance itself notes: "Because of the wide variety of products and their production processes, the

[13] FDA, *Good Importer Practices (Draft Guidance)* (Jan. 2009).

regulatory systems that apply to particular products, and the range of product and importer relationships, it is difficult to develop a set of detailed recommendations that fits every product." Due to these limitations, the guidance cannot be expected to address the specific and unique security considerations inherent in importing specific types of products, such as biopharmaceutical products, intermediates and raw materials. As a result, the document may not have enough detail for various types of importers to develop specific practices that can prevent or detect potential problems at critical points along the product's life cycle.

- Devices and Combination Products – In late April of this year, the agency issued a draft guidance on "Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products."[14] The industry's need was for guidance on getting injector products to market in a compliant, least burdensome manner. However, the draft guidance falls short of meeting this need in a number of ways.[15] In all, we think the agency could have issued a more useful draft of this guidance had it first considered the intended audiences' needs for the guidance.

- Guidance on In Vitro Diagnostic Multivariate Index Assays – As another example, in September 2006, FDA issued a draft guidance on In Vitro Diagnostic Multivariate Index Assays ("IVDMIAs"). In response to an outpouring of comments, the agency held a public meeting to solicit input on the draft guidance and ultimately issued a revised draft guidance on IVDMIAs.[16] Although the public meeting during the comment period was helpful, soliciting input early in the guidance development process – before issuing even the first draft guidance – would have been a better and more efficient approach.[17]

To help remedy this issue, in implementing GGPs 2.0, we suggest that FDA adopt the analogous principles of design controls as it develops guidance.

A robust quality system is important for ensuring the quality, safety, and integrity of drugs, biological products, and devices. In a similar fashion, the agency's GGPs are meant to ensure the agency issues quality guidance that achieves the guidance document's stated purposes.

Taking our analogy a step further: design controls as an element of a quality system ensure that a product meets its specified design requirements. Generally speaking, design

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[14] FDA, *Draft Guidance for Industry and FDA Staff: Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products* (April 2009).

[15] *See e.g.*, Combination Products Coalition, Letter regarding Comments on Draft Guidance for Industry and FDA Staff: Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products; Docket No. FDA-2009-D-0179 (July 23, 2009), available at: http://www.regulations.gov/search/Regs/home.html#documentDetail?R=09000064809f8bbd.

[16] 72 Fed. Reg. 41081, *Draft Guidance for Industry and Food and Drug Administration Staff; In Vitro Diagnostic Multivariate Index Assays; Availability* (July 26, 2007).

[17] *See e.g.*, Letter from the Advanced Medical Technology Association (AdvaMed), Docket Number 2006D-0347: Draft Statement for FDA Public Meeting In Vitro Diagnostic Multivariate Index Assays (Feb. 7, 2007).

controls provide this assurance through various steps, and each of those steps has a counterpart in the guidance development process:

Quality System Design Controls	Guidance Development Processes
1. Design and development planning	Decision-making on the need for guidance
2. Design input, including assessing user requirements	Identifying the needs of the intended audience, including the agency and the public if both are intended
3. Design output	First draft of the guidance
4. Design review	Comment opportunity
5. Design verification and validation	Testing the final draft by allowing agency leadership to review through the prism of the comments and by stakeholder use of the guidance
6. Design transfer	Publication of final guidance document

If we think of guidance document development in these design control terms, the guidance document is actually the ultimate product of a long, rigorous process involving various input, output, and review stages. More specifically, the design input would be the needs of the intended guidance users, and the initial design output could be considered a draft guidance. Further, final design verification and validation cannot be accomplished without consideration of an output that takes into account design review (i.e., stakeholder comments that focus on whether the design output satisfies design input).

Adopting design control principles would particularly help with elements of the guidance development process that have waned over the past several years, such as assessing the needs of the guidance audience, issuing timely guidance that meets those needs, and issuing final guidance that takes into account user comments. As we said before, through the use of GGPs, the agency has made significant improvements over the past 15 years. But in order to ensure that guidance documents disseminate helpful and reliable information to stakeholders, the agency must not lose sight of the importance of a complete guidance development process, including stakeholder transparency and input into that process.

4. *Be transparent in response to comments.*

FDA needs to be transparent in its response to comments when it finalizes a guidance document. Specifically, we believe at least a brief written preamble responding to comments would be very helpful when FDA publishes a final guidance. Such a response would have several important benefits:

- It would help clarify the agency's thinking and help the public better understand the final guidance.

- It would encourage stakeholders to comment in the future.

- And it would help persuade stakeholders to comply because the response would provide a rational basis for compliance and the agency's views, evidencing the fairness of the process.

The agency often asserts that drafting the statement of basis and purpose for final regulations is the source of much delay, because it must be so carefully written to defend against possible litigation. However, a similar statement for guidance should not be nearly as time consuming because it is not part of a rulemaking, and thus cannot be litigated in the same way as a rule.

In sum, we believe the inclusion of at least a general response to comments in the issuance of a final guidance would enhance transparency considerably.

5. *Finalize draft guidance documents.*

We have noticed that some guidance documents remain in draft form interminably. This boils down to a structural problem with guidance development in the sense that FDA has little motivation to finalize guidance because they are not binding anyway and merely reflect the agency's thinking. Unfortunately FDA has no incentive to address comments and issue a final guidance when the agency can apply the guidance while in draft form. Here are a few examples of important guidance documents left in draft for far too long:

- Bioengineered Food -- In January 2001, the agency issued a draft guidance on *Voluntary Labeling Indicating Whether Foods Have or Have Not Been Developed Using Bioengineering*. To date, the agency has not issued a final guidance incorporating comments received on the draft guidance.

- Guidance Drug Adverse Events -- Two guidance documents—one from 2001 and one from 2003—on reporting adverse drug events were left in draft form until they were effectively redrafted in 2008. Those two draft guidances were:

  - Draft guidance for industry entitled "*Providing Regulatory Submissions in Electronic Format-Postmarketing Expedited Safety Report*s" issued in May 2001 (Expedited Reports draft guidance).[18]

  - Draft guidance for industry entitled "*Providing Regulatory Submissions in Electronic Format-Postmarketing Periodic Adverse Drug Experience Reports*" issued in June 2003 (Periodic Reports draft guidance).[19] This new draft guidance is still a draft, 8 years after the first draft was released.

- Other Draft Drug Guidance Documents – We did a quick search of the CDER website and found *64 guidance documents* that were still in draft form *after at least five years, many of which have been in draft form for ten years*. Our list is attached as Attachment

[18] 66 Fed. Reg. 22585, May 4, 2001.
[19] 68 Fed. Reg. 37504, June 24, 2003.

A. Obviously there are many more in draft form for less than five years. We think FDA can do better.

- Combination Products – As an example in the combination products realm, consider the draft GMP guidance, which was issued in September 2004. This agency has even cited this draft guidance in at least one warning letter.[20]

We believe the agency should commit to finalizing its guidance and responding to comments it receives on draft guidance documents. This issue should also be examined in the public meeting we recommended in connection with the lack of guidance discussed above. In addition to identifying the root cause for the agency's tendency not to finalize guidance, we think a partial answer may be to make use of the metrics recommended in the next section.

Further, although not suffering from the same structural problem as with guidance development, for some reason FDA has left many rules in proposed form for far too long. The consequences of leaving a rule in proposed form can be more troublesome than leaving a guidance document in draft form, because a proposed rule leaves the regulated community in greater limbo. While companies need to make choices every day about how they ensure compliance, an unfinished rulemaking leaves them in a quandary. We suggest that FDA adopt a policy of setting an outer limit for how long it will permit a rule to remain proposed before reaching some sort of closure, subject to specific exceptions.

6. *Establish guidance metrics to measure progress.*

We recommend the agency adopt key metrics to assist agency personnel and the public in understanding progress the agency makes in guidance document development. We recommend such metrics include:

- The overall volume of guidance documents published in final, broken down between the two levels and by the issuing office.

- The average duration during which a guidance stays in draft, with further reporting on those that exceed a year, two years, three years, etc.

- The number of pending guidance documents proposed or requested by the public and the average time until they are fully addressed. This metric would also be useful for tracking citizen's petition responses.

- Number of meetings (conference calls, etc.) held with public to discuss guidance development.

Publicly-accessible metrics such as these would provide valuable understanding and insight into the guidance development process.

[20] FDA, Letter to Paul D. Porteous, Dux Industries, Inc. (June 1, 2006).

7. *Be careful not to revert to "podium policy."*

As mentioned above, before the GGPs were implemented, the agency often announced policy during speeches and through individual communications. At a very practical level, that made it difficult for the public and regulated industry to learn about new developments, and created a very uneven understanding of the requirements. After the GGPs, the agency made huge improvements in avoiding such "podium policy." Indeed, the GGPs prohibit the agency from informally communicating new or different regulatory expectations to a broad public audience for the first time.[21] The GGPs have to be followed – i.e., guidance must be used – whenever regulatory expectations that are not readily apparent are first communicated to a broad public audience.[22]

Unfortunately, we have recently experienced and heard about instances where the agency is backsliding into using speeches and letters to announce new policy.[23] This is not the proper form of transparency, and we urge the agency to redouble its vigilance in this area.

8. *Develop realistic guidance plans.*

As part of GGPs, the agency publishes an annual guidance document agenda of possible guidance topics or documents for development or revision during the coming year.[24] This helps create transparency because it allows stakeholders to understand and begin thinking about the agency's planned guidance topics. The public can comment on agency priorities, topics for consideration, and similar issues.

Unfortunately, the annual guidance development plan has not been realistic, and thus not as helpful as it could be. We are concerned that FDA considers this merely a chore, and thus does not embrace the process to the point where the list has real meaning. We would ask the agency to put more thought into the planning process, so that the resulting list has more meaning.

II. TRANSPARENCY IN INDIVIDUAL DECISION-MAKING AND ADJUDICATION

In addition to implementing improvements to transparency in policy-making, the agency must maintain transparency in its individual decision-making.

For a variety of reasons, the public makes use of certain redacted individual decisions released through FOIA or posted to the FDA's website, such as selected inspectional observations, warning letters, product jurisdictional decisions, and approval notices and information. Both at the public hearing FDA held on this transparency topic and in written comments sent so far, various parties are suggesting changes to that system, some to reduce the information and others to expand it. In particular, some of these comments have urged the

[21] 20 CFR § 10.115(e).
[22] *Id.*
[23] This, of course, is distinct from the practice of agency leaders stating their vision and plans – as opposed to policy – for the agency.
[24] 21 CFR § 10.115(f)(5).

agency for greater release of company-specific information. In light of these comments, we want to outline some of the legal background leading up to the agency's current approach in this area. As this background illustrates, protecting this information is necessary to preserve open dialogue between the agency and regulated industry, and its protection need not detract from enhancing transparency.

As you know, The Freedom of Information Act ("FOIA") provides the public with the right to request and gain access to many types of federal agency records or information.[25] All agencies of the Executive Branch of the U.S. Government, which includes FDA, are required to disclose records upon receiving a written request for them, except for those records (or portions of them) that are protected from disclosure by the exemptions and exclusions that apply to certain types of sensitive information. As President Johnson recognized when signing the bill in 1966, FOIA balances the need for public access to information and the need to protect certain categories of information, as "[b]oth are "vital to the welfare of our people."[26] Thus, the FOIA statute provides for several categories of information that are exempt from disclosure because of important public policy reasons. One such exemption is for trade secrets and confidential commercial or financial information.

Consistent with the FOIA statute, FDA regulations balance the presumption of disclosure with protecting information that falls within FOIA's statutory exemptions. Thus, FDA regulations interpret the FOIA statute as requiring the agency to make:

> the fullest possible disclosure of records to the public, consistent with the rights of individuals to privacy, the property rights of persons in trade secrets and confidential commercial or financial information, and the need for the agency to promote frank internal policy deliberations and to pursue its regulatory activities without disruption.[27]

In particular, FDA gains access to a wide variety of sensitive information as a function of its regulatory oversight, including scientific and technical data, product development plans, confidential records reviewed during inspections, and other types of information provided through meetings and routine correspondence. As mentioned above, the public is able to obtain a significant amount of information via the agency's website or through FOIA, including inspectional observations, enforcement letters, approved marketing applications, jurisdictional information, product recalls, and medical product safety events. All of this (and more) information is available even while applicants and regulated organizations are protected from the release of their proprietary information.

In particular, there are long-standing and important public policy reasons for protecting trade secrets and confidential information, one of which is to ensure that regulated industry feels free to engage in open dialogue with federal agencies. For example, when FOIA was enacted over 40 years ago, an accompanying Congressional report explained this exemption as follows:

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[25] 5 USC § 552(l).
[26] Statement by President Johnson, Upon Signing Public Law 89-487 (July 4, 1966).
[27] 21 CFR § 20.20.

> This exemption would assure the confidentiality of information obtained by the Government through questionnaires or through material submitted and disclosures made in procedures. It exempts such material if it would not customarily be made public by the person from whom it was obtained by the Government. The exemption would include … scientific or manufacturing processes or developments . . . . It would also include information which is given to an agency in confidence, since a citizen must be able to confide in his Government. Moreover, where the Government has obligated itself in good faith not to disclose documents or information which it receives, it should be able to honor such obligations.[28]

Importantly, this exemption protects the interests of ***both*** the government and submitters of information. For example, according to the U.S. Department of Justice:

> [The exemption's] very existence encourages submitters to voluntarily furnish useful commercial or financial information to the government and provides the government with an assurance that required submissions will be reliable. The exemption also affords protection to those submitters who are required to furnish commercial or financial information to the government by safeguarding them from the competitive disadvantages that could result from disclosure.[29]

Federal courts have also affirmed the importance of this FOIA exemption in protecting commercial or financial information, including health and safety data submitted to FDA. For example, in *Pub. Citizen Health Research Group v. FDA*, the U.S. Court of Appeals for the District of Columbia has explained that "commercial" information protected under FOIA exemption 4 includes documentation of the health and safety of medical products, because it would be instrumental in gaining marketing approval for the product.[30] At a high level, information considered "commercial" applies when the provider of the information has a commercial interest in the information submitted to the agency.[31] Commercial information goes beyond records that actually reveal commercial operations or relate to income-producing aspects of a business, such as sales statistics, profits and losses, and inventories.[32]

Further, such commercial information is considered "confidential" when it would either impair the government's ability to obtain necessary information in the future or cause substantial

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[28] House Report to accompany S. 1160 (May 9, 1966); *see also* Senate Report to accompany S. 1160 (Oct. 4, 1965).
[29] The Department of Justice Guide to the Freedom of Information Act, at 355 (March 2007).
[30] 704 F.2d 1280, 1290 (D.C. Cir. 1983) (hereinafter "Public Citizen").
[31] *Baker & Hostetler LLP v. U.S. Dep't of Commerce*, 473 F.3d 312, 319 (D.C. Cir. 2006) (hereinafter "Baker & Hostetler").
[32] *Public Citizen* at 1290.

harm to the competitive position of the person from whom the information was obtained.[33] Further, courts have treated information as confidential if it was submitted to the government voluntarily and is of the kind that the provider would not customarily make available to the public.[34] Actual competitive harm is not required; rather, evidence of actual competition and the likelihood of substantial competitive history are sufficient.[35]

In all, FOIA and its exemptions have a long and well-established history.[36] In the context of FDA and stakeholder dialogue, this particular exemption is vital to ensuring free exchange between regulated industry and FDA. For example, as mentioned above, FDA requires access to a wide variety of sensitive information as a function of its regulatory oversight, including scientific and technical data, product development plans, confidential records reviewed during inspections, and information provided through meetings and routine correspondence.

We have provided this background to explain the current law and policy for protecting trade secrets and confidential commercial or financial information that must be maintained as the agency seeks to improve transparency in its decision-making and processes. Importantly, protecting that information will not detract from this transparency and indeed will preserve necessary information exchange between FDA and the regulated industry, and consequently protect the public health.

III. IMPROVEMENTS THAT BRING TRANSPARENCY TO BOTH POLICY DEVELOPMENT AND INDIVIDUAL ADJUDICATION.

a. Enable joint FDA/industry training opportunities.

We think there are many regulatory and compliance topics that would be amenable to joint FDA/industry training. Allowing industry to participate in the training with FDA would not compromise any agency objectives, and would help industry people understand the regulatory issues from the agency's perspective. Topics for such joint training could include:

- Food additive petitions – Due to an absence of guidance, training on agency expectations on content, reasons for non-approval, and next steps in the event of non-approval would be useful in the context of food additive petitions.

- Multi-industry promotional issues – Above we have described promotional issues where guidance would be beneficial. This area could also benefit from joint training, for example, on the recently-published Guidance for Industry on Presenting Risk Information in Prescription Drug and Medical Device Promotion.

- Combination Products – New regulations or proposed regulations, such as the combination product GMP proposed rules, when they are released.

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[33] *Id*. at 1290-91.
[34] *Baker & Hostetler* at 319.
[35] *Public Citizen* at 1291.
[36] Several resources are available for more information on FOIA. *See e.g.*, James T. O'Reilly, *Federal Information Disclosure, 3d* (2009).

- *In Vitro* Diagnostic Products – Current guidance and regulations concerning IVDMIAs and Analyte Specific Reagents ("ASRs").

- Migration Studies – The recent draft guidance on *Assay Migration Studies for In Vitro Diagnostic Devices*.[37]

We believe most industry trade groups would be willing to fund whatever additional expense their participation would create.

b. Provide greater clarity in agency roles and responsibilities.

In many regulatory areas, the lines of responsibility are not clear to those on the outside. While the agency has done a good job of posting organizational charts and personnel lists and making contact information available, FDA should clarify the roles of its staff and who to contact with specific questions or concerns. This would provide a greater degree of transparency to stakeholders who have compliance questions or concerns about certain aspects of FDA regulation. Examples include:

- Safety First and OND/OSE Interactions – There is still some uncertainty regarding the interaction between the Office of New Drugs ("OND") and the Office of Surveillance and Epidemiology ("OSE") staff during drug and biologics reviews. This was partially addressed in the OND/OSE "Safety First" MOU, but is proving to be challenging and confusing in actual implementation.

- Combination Products – FDA should define a clear process for manufacturers to raise suspected instances of inconsistency in the application of GMP regulations to combination products by the FDA field force. In particular, OCP should specify who at the agency will address inconsistency issues and should ensure that all relevant agency components are involved and informed of the outcome.

[37] FDA, *Draft Guidance Assay Migration Studies for In Vitro Diagnostic Devices* (Jan. 5, 2009).

CONCLUSION

The CPC commends the agency for undertaking this initiative to improve the transparency of agency processes and decisions. This is an exciting time for the public and, we hope, the agency, as we both strive to improve patient care through safe, effective, and innovative products and safeguard the food supply. We look forward to working with the agency on these important improvements.

Respectfully submitted,

Bradley Merrill Thompson, on behalf of the
Combination Products Coalition

ATTACHMENT A

CDER GUIDANCE STILL IN DRAFT FORM AFTER AT LEAST 5 YEARS

1.	Accelerated Approval Products: Submission of Promotional Materials	*Draft*	3/26/1999
2.	Product Name Placement, Size, and Prominence in Advertising and Promotional Labeling	*Draft*	1/1999
3.	Consumer-Directed Broadcast Advertising of Restricted Devices	*Draft*	1/26/2004
4.	"Help-Seeking" and Other Disease Awareness Communications by or on Behalf of Drug and Device Firms	*Draft*	1/26/2004
5.	Brief Summary: Disclosing Risk Information in Consumer-Directed Print Advertisements		
	Labeling Example	*Draft*	2/4/2004
	Labeling Example; Consumer-Friendly Version		
6.	Analytical Procedures and Methods Validation.	*Draft*	8/2000
7.	Comparability Protocols -- Chemistry, Manufacturing, and Controls Information	*Draft*	2/2003
8.	Drugs, Biologics, and Medical Devices Derived from Bioengineered Plants for Use in Humans and Animals	*Draft*	9/11/2003
9.	Interpreting Sameness of Monoclonal Antibody Products Under the Orphan Drug Regulations	*Draft*	7/24/1999
10.	Liposome Drug Products: Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation.	*Draft*	7/2002
11.	Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products	*Draft*	11/13/1998
12.	SUPAC-SS: Nonsterile Semisolid Dosage Forms Manufacturing Equipment Addendum	*Draft*	12/1998

13. Acute Bacterial Meningitis — Developing Antimicrobial Drugs for Treatment	*Draft*	7/22/1998
14. Acute or Chronic Bacterial Prostatitis — Developing Antimicrobial Drugs for Treatment	*Draft*	7/22/1998
15. Bacterial Vaginosis — Developing Antimicrobial Drugs for Treatment	*Draft*	7/22/1998
16. Catheter-Related Bloodstream Infections - Developing Antimicrobial Drugs for Treatment	*Draft*	10/1999
17. Complicated Urinary Tract Infections and Pyelonephritis — Developing Antimicrobial Drugs for Treatment	*Draft*	7/22/1998
18. Developing Antimicrobial Drugs — General Considerations for Clinical Trials [Main Document]	*Draft*	7/22/1998
19. Developing Antimicrobial Drugs to Treat Inhalational Anthrax (Post Exposure) --	*Draft*	3/15/2002
20. Empiric Therapy of Febrile Neutropenia — Developing Antimicrobial Drugs for Treatment	*Draft*	7/22/1998
21. Evaluating Clinical Studies Of Antimicrobials In The Division Of Anti-Infective Drug Products	*Draft*	2/18/1997
22. Lyme Disease — Developing Antimicrobial Drugs for Treatment	*Draft*	7/22/1998
23. Nosocomial Pneumonia — Developing Antimicrobial Drugs for Treatment	*Draft*	7/22/1998
24. Secondary Bacterial Infections of Acute Bronchitis — Developing Antimicrobial Drugs for Treatment	*Draft*	7/22/1998
25. Streptococcal Pharyngitis and Tonsillitis — Developing Antimicrobial Drugs for Treatment	*Draft*	7/22/1998
26. Uncomplicated and Complicated Skin and Skin Structure Infections — Developing Antimicrobial Drugs for Treatment	*Draft*	7/22/1998
27. Uncomplicated Gonorrhea — Developing Antimicrobial Drugs for Treatment	*Draft*	7/22/1998,
28. Uncomplicated Urinary Tract Infections —	*Draft*	7/22/1998

Developing Antimicrobial Drugs for Treatment		
29. Vulvovaginal Candidiasis — Developing Antimicrobial Drugs for Treatment	*Draft*	7/22/1998
30. Allergic Rhinitis: Clinical Development Programs for Drug Products	*Draft*	6/2000
31. Clinical Development Programs for Drugs, Devices, and Biological Products Intended for the Treatment of Osteoarthritis	*Draft*	7/07/1999
32. Clinical Evaluation of Lipid-Altering Agents	*Draft*	10/1990
33. Development of Parathyroid Hormone for the Prevention and Treatment of Osteoporosis	*Draft*	5/2000
34. Drugs, Biologics, and Medical Devices Derived from Bioengineered Plants for Use in Humans and Animals	*Draft*	9/6/2002
35. Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms — Recommendations for Clinical Evaluation	*Draft*	1/2003
36. Exercise-Induced Bronchospasm (EIB) — Development of Drugs to Prevent EIB	*Draft*	2/2002
37. Female Sexual Dysfunction: Clinical Development of Drug Products for Treatment	*Draft*	5/2000
38. Inhalation Drug Products Packaged in Semipermeable Container Closure Systems	*Draft*	7/2002
39. OTC Treatment of Herpes Labialis with Antiviral Agents	*Draft*	3/8/2000
40. Pediatric Oncology Studies In Response to a Written Request	*Draft*	6/2000
41. Preclinical and Clinical Evaluation of Agents Used in the Prevention or Treatment of Postmenopausal Osteoporosis	*Draft*	4/1994
42. General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological	*Draft*	11/1998

Products		
43. Comparability Protocols - Protein Drug Products and Biological Products - Chemistry, Manufacturing, and Controls Information	*Draft*	9/3/2003
44. Current Good Manufacturing Practice for Medical Gases	*Draft*	5/6/2003
45. Manufacturing, Processing, or Holding Active Pharmaceutical Ingredients	*Draft*	4/17/1998
46. Powder Blends and Finished Dosage Units — Stratified In-Process Dosage Unit Sampling and Assessment	*Draft*	11/2003
Revised Attachments		
47. Providing Regulatory Submissions in Electronic Format -General Considerations (Issued, Posted 10/22/2003)	*Draft*	10/2003
48. Providing Regulatory Submissions in Electronic Format - Prescription Drug Advertising and Promotional Labeling	*Draft*	1/2001
49. Labeling for Combined Oral Contraceptives	*Draft*	3/2/2004
50. Labeling Guidance for OTC Topical Drug Products for the Treatment of Vaginal Yeast Infections (Vulvovaginal Candidiasis)	*Draft*	6/1998
51. Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions	*Draft*	1/2004
52. PET Drug Applications - Content and Format for NDAs and ANDAs		
Sample formats for chemistry, manufacturing, and controls sections	*Draft*	3/7/2000
Sample formats for labeling		
Sample formats for Form FDA 356h		
Sample formats for user fee Form FDA 3397		

53. Integration of Study Results to Assess Concerns about Human Reproductive and Developmental Toxicities (Issued , Posted 11/9/2001)	*Draft*	11/2001
54. Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals	*Draft*	5/2001
55. Applications Covered by Section 505(b)(2)	*Draft*	10/1999
56. Disclosing Information Provided to Advisory Committees in Connection with Open Advisory Committee Meetings Related to the Testing or Approval of New Drugs and Convened by the Center for Drug Evaluation and Research, Beginning on January 1, 2000	*Draft*	12/1999
57. Disclosure of Conflicts of Interest for Special Government Employees Participating in FDA Product Specific Advisory Committees	*Draft*	2/14/2002
58. Forms for Registration of Producers of Drugs and Listing of Drugs in Commercial Distribution	*Draft*	5/14/2001
59. Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions	*Draft*	1/2004
60. Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines	*Draft*	3/9/2001
61. Submitting Debarment Certification Statements	*Draft*	10/2/98
62. Submitting Marketing Applications According to the ICH/CTD Format: General Considerations	*Draft*	9/5/2001
63. The Use of Clinical Holds Following Clinical Investigator Misconduct	*Draft*	4/2002
64. Attachment G -- Draft Interim Guidance Document for Waivers of and Reductions in User Fees	*Draft*	7/16/1993