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December 1, 2011

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

Re: Docket No. FDA-2009-N-0247; FDA Transparency Initiative: Draft Proposals for Public Comment to Increase Transparency By Promoting Greater Access to the Agency's Compliance and Enforcement Data

Dear Sir or Madam:

The Combination Products Coalition ("CPC") commends the U.S. Food and Drug Administration ("Agency") for its efforts to increase transparency with regard to Agency regulation and enforcement. As an organization focused on the advancement of combination product policy development, the CPC wholeheartedly supports transparency throughout the Agency and specifically in the area of combination product compliance and enforcement. We would be delighted to see the Agency's transparency initiatives include combination products, and we believe there are numerous opportunities to do so. In this regard, below we offer our thoughts on how the Agency's Transparency Initiative should encompass combination products and how combination product issues can be incorporated into the Agency's *Draft Proposals for Public Comment to Increase Transparency By Promoting Greater Access to the Agency's Compliance and Enforcement Data*.

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.

To date, the Agency seems to have not incorporated combination products directly into its transparency initiatives and proposals. Yet, as an area in which regulation and policy are still in the early stages of development, transparency here is particularly

important. Access to compliance and enforcement examples offers stakeholders an opportunity to understand the application of new and existing combination product regulations and policies, thereby enhancing these stakeholders' understanding and their own compliance. Below we offer suggestions on how the Agency could accomplish this much-needed transparency.

1. GENERAL COMMENTS: THE TRANSPARENCY INITIATIVE & COMBINATION PRODUCTS

From a regulatory standpoint, combination products – products that involve the convergence of two or more different types of FDA-regulated articles (drugs, medical devices, and biological products) – are regulated articles that have their own unique regulatory scheme, just as pharmaceuticals, medical devices, and biological products do. From a patient health standpoint, combination products represent promising advances in patient care. Patients suffering from numerous types of serious diseases and conditions have already benefited from combination products, and many more innovative and beneficial combination products are currently being researched and developed. Industry estimates reflect this growth and development.

As regulated articles subject to their own regulatory framework and policy development, combination products should be included within Agency-wide initiatives, absent a specific and valid reason not to include them. In this regard, the Agency's Transparency Initiative should encompass combination products as articles regulated by the Agency. Thus, although we are pleased the Agency has created the Transparency Task Force and proposed actions to increase transparency, we are concerned that to date, the Task Force has not addressed transparency for combination products.

For example, 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.¹ To take a more tactical 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.²

As another example, 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.³

¹ See FDA Transparency Initiative: Improving Transparency to Regulated Industry 11-17 (January 2011).

² The product areas include: foods, cosmetics, dietary supplements, medical devices, radiological, animal veterinary, drugs, tobacco, and biologics.

³ 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

However, we see several opportunities within the Task Force's draft proposals for compliance and enforcement data that could address transparency as related to combination products.

2. SPECIFIC COMMENTS

- a. **DRAFT PROPOSAL 1** – *FDA should explore different ways to improve data quality and facilitate more timely data disclosure by expediting data entry, expediting inspection review and classification, and/or updating the data more frequently. Tools to improve data quality and speed data disclosure may include, for example, providing new technologies to investigators, introducing other process improvements, and/or implementing administrative incentives. To implement these types of tools effectively, FDA also should explore how frequently data should be updated in order for it to be useful to stakeholders.*

The FDA has frequently stated that it wants industry to learn from inspections of peer companies. We agree. To achieve this goal, industry requires timely access to relevant compliance and enforcement data. Unfortunately, presently the majority of compliance and enforcement data published by FDA is neither timely nor detailed enough to allow industry to learn from inspections of their peers. The annual updating of inspectional outcomes on the FDA website is of limited value, as is providing only the most common inspection observations based on the Turbo-EIR language. For example, deficient investigations (21 C.F.R. § 211.192) have been a problematic category of observations for many years, but without additional information regarding which types of investigations were deficient (e.g., CAPA, OOS, customer complaints), the value of this information is limited.

We urge the Agency to focus on providing actual redacted Form FDA-483s as soon as possible after the close of inspections. We recommend that FDA establish a goal to provide compliance and enforcement data – including redacted FDA-483s – on at least a weekly basis, similar to the current posting of warning letters.

As a related matter, the usefulness of the compliance and enforcement data should be highly prioritized over the aesthetics of *how* the data are presented. In this regard, we recommend that instead of endeavoring to provide additional graphics, the Agency provide additional detail on compliance and enforcement activities. For example, posting redacted FDA-483s alongside each published official inspection classification.

Finally, we suggest the Agency minimize *analysis* relative to the specific deficiencies. Not only will this help conserve resources, the analysis often is something individual companies or trade publications should provide. In contrast, only FDA has the ability to provide access to most compliance and enforcement information.

- b. DRAFT PROPOSAL 4** – *FDA should explore whether it can better integrate its compliance and enforcement data, as well as its other publicly available data on regulated firms, to make the data more user-friendly and easier to analyze.*

We appreciate the Agency's desire to make compliance and enforcement data more user friendly and easier to analyze. However, FDA should prioritize its limited resources on identifying and making information available online, rather than on how to better present the limited data that are already available. Then, if additional resources exist or subsequently become available, FDA can consider how best to present this information in a more user-friendly manner.

- c. DRAFT PROPOSAL 5** – *FDA should explore whether additional, or more specific search criteria (e.g., criteria that would enable individual product-specific or violation-specific searches), or more sophisticated search capability (e.g., predictive name searches) would make the inspections database more user-friendly and the data easier to analyze.*

We encourage the Agency to add whether or not a search result is associated with a combination product to the criteria by which the FDA website and databases can be searched, as part of Draft Proposal 5. We understand that there is an existing field within the Agency's internal databases indicating whether a submission is related to combination products. It would be helpful if the Agency included this field in public databases and allowed the public to search using this field. We are pleased with the Agency's recent revisions to the Premarket Notification⁴ and the Premarket Approval databases⁵ to allow searching by whether the product is a combination product. This capability provides combination product manufacturers with additional insight into the nature of the filings required when seeking approval of a new combination product or when making changes to an existing product.

However, presently this search feature is not available for all FDA databases, and we request the Agency revise the database to incorporate this search field. In particular, including whether a product is a combination product in the Adverse Event Reporting System data files and making this a searchable field in the MAUDE database would help combination product manufacturers determine who the responsible party may be with respect to post-market safety reporting. It also would be beneficial to allow the public to search Warning Letters by whether the deficiencies related to combination products as this would provide additional insight into the Agency's interpretation of how the drug, device and biological product regulations apply to combination products.

- d. DRAFT PROPOSAL 6** – *FDA should explore whether posting additional data compilations or analysis, such as the Agency's common inspection observations or warning letter compilations, both of which it already*

⁴ See <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm>.

⁵ See <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm>.

posts, would increase transparency or better inform the Agency's own compliance efforts.

With respect to Draft Proposal 6, we support FDA posting additional data compilations or analysis that specifically relate to combination products. Although the CPC commends the recent creation of the public inspection classification database, it does not appear to provide information as to whether a given inspection involved combination products, nor does it seem to permit any searches based on a product's status as a combination product.⁶ Similarly, the Inspectional Observation summaries that were recently released do not denote when a product was a combination product or a constituent part of a combination product.^{7,8}

At the same time, we request FDA provide actual, raw data as a priority over compilations or analysis. We agree that FDA's analysis is useful; however, the priority should first be identifying and enabling access to the underlying raw data (e.g., redacted FDA-483s). This approach also would enable outside parties to conduct the analysis, thus freeing FDA resources.

3. PRIOR CPC COMMENTS

We would like to put a point of emphasis on these comments. And there's an irony here that we just have to point out. Since at least 2004, the CPC has been advocating that FDA increase transparency by sharing on its website more data around compliance and enforcement with regard to combination products. While we have taken just about every opportunity we could find to express that point of view including several meetings with the agency, here are a few examples of letters we have written to the agency on this point (copies attached with the relevant language highlighted):

- On December 3, 2004, we filed comments on FDA's Draft Guidance on Good Manufacturing Practices for Combination Products, and in that comment letter we specifically asked the agency to expand the types of enforcement data it posts on its website.
- On July 5, 2006, we sent a letter to the then director of the Office of Combination Products again urging the office to increase the types of enforcement and compliance data posted to the website relating to GMP inspections.
- On August 7, 2009, we sent a comment letter in response to this same transparency initiative, discussing the types of redaction necessary in order to post inspection-related data on the agency's website.
- On June 20, 2011, we sent a letter to Commissioner Hamburg, and copied the transparency initiative docket, expressing much concern that the

⁶ <http://www.accessdata.fda.gov/scripts/inspsearch/>.

⁷ <http://www.fda.gov/ICECI/EnforcementActions/ucm250720.htm>.

⁸ This is not intended to be an exhaustive list of the databases we think would benefit from including this as a searchable field; however, these are in our opinion the highest priority.

transparency initiative to date had completely ignored combination products. In that letter, on page 7, we again reiterated our desire to see more enforcement related data posted to the website with regard to combination products.

So after urging the agency for seven years to expand the amount of enforcement-related data available on the website with regard to combination products, imagine how disheartening it was to see the agency's proposal for expanding enforcement data available on the website for everything but combination products. We are, of course, well aware that the combination product data will be mixed in with everything else because combination products, after all, are drugs, devices and biological products. But without some search feature tailored to combination products, that's like finding a needle in a haystack. It really does us no good.

* * *

In summary, we believe the Agency should ensure access to compliance and enforcement information for combination products just as it's provided for other types of regulated articles.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Bradley Merrill Thompson". The signature is fluid and cursive, with a large initial "B" and "M".

Bradley Merrill Thompson,
On behalf of the Combination Products Coalition

cc:

Jill Warner, Associate Commissioner (Acting), Office of Special Medical Programs
Think Nguyen, Director, Office of Combination Products



CPC

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December 3, 2004

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**RE: Comments on Draft Guidance for Industry and FDA: Current
Good Manufacturing Practice for Combination Products, Food
and Drug Administration Docket No. 2004D-0431**

Dear Sir or Madam:

The Combination Products Coalition ("CPC") respectfully submits for consideration these comments on the Food and Drug Administration's ("FDA") Draft Guidance on Current Good Manufacturing Practice for Combination Products (the "Draft Guidance"). The CPC is a group of leading pharmaceutical, biologics, and medical device manufacturers with substantial experience in the combination products arena, as well as in each of the constituent technologies. Because of its diverse membership, the CPC brings a uniquely broad and experienced perspective to the problems of regulating combination products. With that background in mind, we offer the following comments.

I. General Comments

The CPC applauds the FDA's effort in crafting this Draft Guidance, which provides a good start to tackling the difficult problems that arise with application of Current Good Manufacturing Practices ("CGMP") and Quality System ("QS") regulations to combination products. We believe the Draft Guidance, which approaches the issues from the

"hundred-thousand foot" level, is the right place to begin the complex task of working through the plethora of issues raised by applying two or more distinct sets of regulations to one product. It is the beginning, however, not the end. With the diverse array of combination products that fall within the agency's scope, the only way for FDA to achieve consistency in application of CGMP and QS regulations is to develop a number of specific guidances to address the variety of issues raised. With that in mind, we urge FDA to continue its efforts, and to develop more specific guidance on application of CGMP and QS regulations to combination products.

That said, the purpose of these comments is to identify specific areas in which FDA's approach needs further clarification or revision. Our goal is to ensure predictable, transparent, and consistent application of the guidances that ultimately apply to the manufacturing of combination products. To that end, we offer the following specific comments.

II. Specific Comments

A. FDA needs to clarify impact of assignment on application of CGMP and QS regulations

One of the most critical issues impacting application of CGMPs and QS regulations to combination products is whether, and to what extent, FDA will allow assignment of a lead center to drive the determination of what CGMPs and QS regulations should apply to a particular combination product. As discussed in the CPC's *Response to Request for Comment on Primary Mode of Action* filed with the FDA on August 18, 2004,¹ and raised again in the CPC's comments on the *Draft Guidance for Industry and FDA Staff: Application User Fees for Combination Products*, filed with the agency on November 24, 2004, we believe that FDA needs to clarify its view of what assignment to a particular agency component means before FDA proceeds with issuing further regulations or guidance. If FDA adopts the view that assignment determines not only who will take the lead, but also which authorities and obligations will apply, that has tremendous implications on downstream regulation. The application of good manufacturing and quality systems regulations are just the start – albeit an important one.

The Draft Guidance provides a good example of the impact that the assignment issue can have in practice. Although it is not clear from the Draft Guidance what role the FDA intends the lead center to play in determining which regulations will apply to a given combination product, the Draft Guidance seems to suggest that FDA intends for the lead center to oversee regulation of a combination product. Presumably, that could include determination of which manufacturing and quality system regulations apply. However, the Draft Guidance also allows that compliance with CGMPs and QS regulations can generally be achieved "by using the current good manufacturing practice system already operating at a manufacturing facility."² Indeed, under the Draft Guidance, the manufacturer's pre-existing current good manufacturing practice system (referred to in the Draft Guidance as the "Operating Manufacturing Control System") would be a major factor in deciding which regulation sets the overall, general quality system for a particular

combination product. The other regulations would be incorporated in a subordinate capacity to address specific issues that may be pertinent to one of the product's components.³ Giving the lead center ultimate authority over regulations applicable to the manufacturing of a combination product very well could negate this provision – which is the foundation of the guidance's approach. Instead, the lead center for each combination product would control. Consider the potential inconsistencies:

- For a device manufacturer that manufactures a drug/device combination product, the Operating Manufacturing Control System in place likely would be based on QS regulations applicable to medical devices. Scale up of those manufacturing facilities, therefore, would likely be handled under the device regulations, and no filing may be required.
- If however, CDER is assigned as lead center for the drug/device combination and given ultimate control over regulation, CDER might require that scale-up of the manufacturing facilities be handled under the drug authorities. If so, CDER could require the manufacturer to file a supplemental NDA to accommodate the change.

This need not be the case, though. FDA has made very clear that, although the statute provides a mechanism for determining which agency component will take the lead on review of a particular combination product, it did not provide a similar mechanism for determining which regulatory authorities will apply. Instead, Congress chose to rely on FDA's expertise to determine which regulatory authorities should apply to a given combination product.⁴ We urge FDA not to take that responsibility lightly.

With that in mind, the CPC disagrees strongly with allowing assignment to a lead center to control the complex question of which regulations apply downstream, and believes that such a determination would lead to inconsistent and unintended outcomes. For this reason, we exhort FDA to make a clear and unambiguous statement of its intent.

B. FDA should reconsider its case-by-case approach to regulation of specific combination products

Generally, we believe that FDA's case-by-case approach to regulation of specific combination products outlined in the Draft Guidance misses the mark. FDA has stated time and again that it intends to develop regulations and guidance that ensure consistency, predictability and transparency of combination product regulation. The outlined approach cannot achieve that goal. With the wide variety of combination products to be covered by the Draft Guidance, and thousands of custom-tailored systems likely to result, there is an incredible potential for disparity in regulatory treatment among similar combination products. In addition, without more direct and specific guidance, word of mouth among reviewers and investigators may lead to misapplication of similar, generalized principles to very different combination products.

We understand and appreciate that, in the world of combination products, one size does not fit all. In fact, in our white paper submitted to FDA in April 2004,⁵ the CPC commented on the need for flexibility in defining quality systems and good manufacturing practice requirements for various types of combination products, since each combination is different and may involve widely different development and production processes. However, the current approach goes too far, exchanging flexibility for customization. Instead, we recommend that FDA develop specific guidance to address the particular manufacturing and quality systems issues that arise with different types of combination products. The only way to ensure consistency, predictability and transparency is to specify the rules. Only then can manufacturers be assured that: (1) They know and are complying with the rules; and (2) they are complying with the same rules as their competitors.

1. At the very least, FDA should consider putting procedural safeguards in place

Although we strongly believe that FDA's current approach fails to meet FDA's goals, we understand that FDA may disagree with our assessment. For that reason, should FDA continue down the path described in the Draft Guidance, we offer the following suggestions.

If FDA follows the case-by-case approach enumerated in the Draft Guidance, the agency needs to elaborate a set of basic procedural norms that will be followed in all such discussions. This will provide at least some level of assurance to manufacturers that they are on a level playing field and promote public confidence in the integrity of combination-products regulation.

To that end, we believe that, at a bare minimum, the Draft Guidance needs to provide additional procedural detail to clarify how this process might work for various types of combination products. For instance: What are the specific pathways for initiating and conducting these discussions? How can sponsors ensure they are involved in all relevant discussions with FDA staff? What data and submissions may be required for different products that involve different combinations of the regulations? What information will FDA require a manufacturer to submit in support of its proposed CGMP/QS plan? What are the standards for determining the adequacy of manufacturers' proposals? Are there indicative time lines for processing manufacturers' requests? What are the end-points of these discussions, e.g., will the results of these discussions be memorialized in a letter of agreement or other record on which manufacturers can rely in planning their ongoing operations? FDA should include guidance to address all of these questions.

We recognize that the diversity of combination products makes it very hard to outline a single procedural pathway that will be appropriate in every instance. With that in mind, to clarify the appropriate procedures for conducting discussions between FDA and

manufacturers, it may be necessary for the Draft Guidance to elaborate multiple pathways and criteria for determining which combination products appropriately belong on which procedural pathway. The Draft Guidance should consider a number of indicative example products, clarify how these procedures might actually work for each of them, and enunciate the key factors FDA will consider in determining what process is appropriate for a given combination product.

In addition, to ensure at least some level of transparency in the process, we encourage FDA to publish its CGMP/QS decisions, with as much supporting documentation as possible. While we understand that confidentiality concerns may prevent sharing of all of the information exchanged between manufacturers and FDA, it is critical that FDA provide easy access to at least basic information to give the industry a sense of how FDA might apply the rules in a given circumstance. Along these same lines, we suggest that FDA provide an interactive webpage for manufacturers, with a feature that enables manufacturers to ask FDA questions, and receive answers. Posting of questions and answers on the webpage would provide an additional opportunity for bringing transparency to the process.

C. FDA should specify which regulations will apply to different types of combination products

We believe that FDA's simultaneous application of CGMPs and QS regulations to combination products is unnecessary and impractical to achieve. Instead, we believe that FDA should: (1) Apply appropriate regulations to *each constituent component* of the combination product as long as the manufacturer can distinguish between the components of the product; and (2) if constituent components become indistinguishable (which may happen with respect to some integral combination products that are formed into a unit), specify which of the CGMP regulations and which of the QS regulations will apply to that type of combination product. We discuss this approach in greater detail below.

1. FDA should apply the appropriate regulations to each constituent component as long as they are distinguishable

We believe that FDA should apply the appropriate regulations to each constituent component of a combination product – even if the products are joined together – as long as the constituent components remain distinguishable. As currently written, the Draft Guidance applies device QS regulations to device components and drug CGMPs to drug components, until the components become one. The Draft Guidance provides that, for integral and kit combination products, “both sets of current good manufacturing practice regulations are applicable during and after joining the constituent parts together.”⁶

The concept of “during and after joining,” while simple on its face, assumes too much. It assumes that there is some clear point at which the constituents of a combination product merge, and that only at that point do both

regulatory schemes become relevant. In practice, however, there may not be a finite point in time at which the constituents join as a product. Instead, they may retain their individual constituent character throughout the manufacturing process (as in the case of virtual combination products and some kits).

- For example, the constituent components of a drug and delivery system – such as an IV pump -- can maintain their individual constituent character, even after being combined.

Conversely, the nature of the constituent parts may trigger consideration of *both* regulatory schemes even *prior to joinder*. Consider how this example from FDA's archives might be handled:

- FDA determined that, although a catheter flush solution containing a blood-thinning drug and an antibiotic combined with a catheter had a primary mode of action that was "physical in nature," and typically would be subject to review by CDRH, the innovative aspects of the solutions raised important scientific and regulatory questions that were more appropriately reviewed by CDER.⁷ FDA had clinical investigations of the product proceed under the investigational drug provisions of the statute. Since the combination product was being treated as a drug – would drug CGMPs control, or would QS regulations (including design controls) apply to the catheter component?

As this example illustrates, if it is known that a given constituent is destined to be "joined" into a particular combination product, it may be necessary to take certain steps even before any such joinder, to lay the groundwork for compliance with regulatory requirements that will later come into force. Given these practicalities, the concept of "during and after joinder" may be too simple to work in practice.

As an alternative, we believe that FDA should provide for appropriate regulation of each of the constituent components, as long as they are distinguishable. What is *appropriate*, however, should depend on the type of combination product involved. In many (likely most) cases, a device component should be subject only to device QS regulation until such time as the device is no longer distinguishable from the other constituent components of a combination product. Depending on the nature of the combination product, *appropriate* regulation may require the incorporation of certain regulations from the drug CGMP scheme to ensure patient safety of the ultimate combination product. We do not advocate duplicative or parallel regulation; rather, we encourage FDA to choose appropriate regulations depending on the type of combination product involved.

As discussed in our April 2004 White Paper, a case-study approach may be the best way to identify and address these subtleties. This would involve looking at development and production processes for various example products,

considering the CGMP/QS issues that may arise at various points in these processes, and specifying the appropriate combination of regulations that apply at various stages. Again, this requires much more specific guidance than FDA has provided in the DRAFT Guidance

2. If constituent components become indistinguishable, specify which of the CGMP regulations and which of the QS regulations will apply

Even when there may be a temptation to apply dual CGMP and QS requirements to a particular combination product – as when the components become indistinguishable -- we believe FDA must make choices among which regulations should apply. Attempting to mesh the CGMP regulations and QSR requirements into one common regulatory scheme is tantamount to fitting a square peg into a round hole. It ignores the purpose and shape of the underlying regulations. For instance, the device QS regulations reach farther “upstream” into the design process than the drug CGMP regulations reach. As a result, manufacturers otherwise subject to CGMP regulation may find that their existing Operating Manufacturing Control Systems do not have appropriate upstream “slots” into which the device requirements can be fit. Blanket application of both sets of regulations may provide a simple answer, but it falls short in implementation. FDA needs to choose which regulations will apply, under what circumstances.

Once again, we believe that the answer is to provide specific guidance on which QS and which CGMP regulations apply to particular types of combination products. Using case studies and examples, FDA could go a long way toward simplifying the process for the agency and industry alike.

D. Training and Personnel Development

As discussed in our April 2004 White Paper, because of the complexity of the different CGMP and QSR systems for biologics, drugs and devices, appropriate regulation and enforcement of combination products will require cross-training of inspectors, or in some instances, inspection by a team of two or more inspectors with complementary skills and experience. The Draft Guidance does not yet address the important question of how compliance inspections may differ for different types of combination products: *e.g.*, What are likely to be the criteria for determining whether a given CGMP/QSR system can be adequately inspected by a single inspector with cross-training, as opposed to needing separate inspections of its CGMP and QSR components? Will the “lead” inspection personnel vary, depending on the assignment of the lead center for regulating a particular combination product? How will the FDA ensure consistent treatment of similar products? What role can manufacturers usefully play in developing appropriate solutions and in exchanging ideas related to training and development of personnel? These questions should be addressed in, or in parallel with, the Draft Guidance.

III. Conclusion

We appreciate FDA's efforts in preparing this Draft Guidance, and believe it is the right place to start. The next step, however, is critical. We firmly feel that FDA needs to provide more specific guidance on how CGMP and QS regulations will be applied to particular types of combination products, using case studies and examples to illustrate the agency's thinking. FDA has a tremendous opportunity to use its scientific expertise and experience to craft thoughtful and practical guidelines that will ensure consistent and predictable application of the regulations. This should be familiar ground for FDA, and we urge the agency to take this step. We stand ready to assist in any way we can.

We appreciate this opportunity to present our comments on the Draft Guidance, and look forward to working with FDA as the agency moves forward.

Respectfully Submitted,



Bradley Merrill Thompson
For the Combination Products Coalition

¹ (Letter from Bradley Merrill Thompson, Combination Products Coalition, to FDA of August 18, 2004, regarding Response to Request for Comment on Primary Mode of Action, Food and Drug Administration Docket Number 2004N-0194).

² FDA, *Guidance for Industry and FDA, Current Good Manufacturing Practice for Combination Products*, at 5 (September 2004).

³ See Draft Guidance at 6, Table 1.

⁴ See *Final Rule, Regulations Restricting the Sale and Distribution of Cigarettes and Smokeless Tobacco to Protect Children and Adolescents*, 61 Fed. Reg. 44396, 44400 (August 28, 1996) (Discussing in general FDA's discretion to determine which regulatory authorities apply to combination products).

⁵ Combination Products Coalition, *Combination Products: Proposed Policies to Enhance the FDA Regulatory Process* (Submitted to the FDA in April, 2004).

⁶ Draft Guidance at 5.

⁷ Final Tobacco Rule, 61 Fed. Reg. at 44403.



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July 5, 2006

Mr. Mark D. Kramer
Director, Office of Combination Products
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Re: Increasing Transparency in the Application cGMP Regulations to
Combination Products

Dear Mr. Kramer:

Thank you very much for meeting with the Combination Products Coalition (“CPC”) on May 4, 2006, with regard to the status of various initiatives at the Office of Combination Products (“OCP”). We found the meeting to be tremendously helpful and productive, and we appreciate you and the other OCP representatives taking time to meet with us.

During the meeting, certain representatives of the OCP mentioned that they would be interested in the CPC’s suggestions for bringing greater transparency to the application of current Good Manufacturing Practices (“cGMP”)¹ regulations, and for ensuring consistency in enforcement issues, as these regulations are applied to combination products.

By way of background, the CPC is comprised of leading pharmaceutical, biological, and medical device manufacturers that have considerable experience with combination products, as well as their constituent product areas. We think that our

¹ For purposes of this letter, the term *current good manufacturing practice* refers to the current good manufacturing practice regulations for drugs and most biological products under 21 CFR Parts 210 and 211, for certain biological products under 21 CFR Parts 600-680, and the quality system regulations for devices under 21 CFR Part 820.

diverse membership allows us to bring a uniquely broad perspective to the issues facing the regulation of combination products, such as the application of cGMP regulations. With that background in mind, we offer the following thoughts and suggestions with regard to these issues.

I. General Suggestions

Without a doubt, one of the biggest concerns of an FDA-regulated manufacturer is regulatory compliance. Manufacturers want to comply with FDA regulations that apply to them for a variety of reasons, not the least of which is that a high level of compliance helps to ensure a high quality product that health professionals and patients can use safely and reliably.

In order to achieve a high level of compliance, though, manufacturers must first thoroughly understand how the regulations apply to them. Understandably, when cutting-edge technologies are concerned, the application of existing regulations and standards can be unclear or even downright confusing. Also understandably, crafting new policies and regulations can be a painstaking process that takes a tremendous amount of time and effort on behalf of both industry and FDA. Both applying the existing cGMP regulations to combination products, as well as drafting new rules for such products, are no exceptions. We understand that currently FDA predicts that a proposed rule on combination product cGMP is expected in the spring of 2007, and we would guess that a final rule is some years away.

While FDA is developing new regulations, though, manufacturers still need to comply with existing regulations. Therefore, the CPC believes that the agency should implement tools to facilitate understanding of the application of existing cGMP regulations to combination products. We describe our specific suggestions in detail below.

II. Specific Suggestions

A. Web-Based Information

Through its website, the OCP shares a wealth of information with regard to the request for designation (“RFD”) process and jurisdictional decisions.² Frankly, we have found this information to be extremely helpful in determining which FDA Center is the “lead” for a particular product and for developing RFDs. In a similar vein, we believe that analogous information with respect to the application of cGMP regulations to combination products would be tremendously useful in helping industry achieve compliance with the appropriate cGMP regulations. More specifically, the CPC suggests that the OCP post on its website the following information with regard to the application of cGMP regulations:

² See FDA, OCP, Jurisdictional Updates, *available at*: <http://www.fda.gov/oc/combination/updates.html>.

- GMP Updates – This would consist of in-depth summaries of past decisions addressing how cGMP regulations apply to combination products.
- Agency Decisions – The agency should post redacted agency decisions concerning the applicability of cGMP regulations to combination products. “Agency decisions” are what a firm receives from FDA regarding cGMP issues as applied to combination products, for example, warning letters, informal correspondence such as meeting minutes, and advisory opinions.³
- GMP Determinations – This would consist of one-line summaries of decisions the agency has made with regard to the applicability of cGMP regulations to individual combination products.
- Pertinent guidance documents and other FDA documents, for example, manual updates.

We also believe that this information has the advantage of being readily accessible to FDA for sharing. While in some cases FDA would need to draft summaries and redact information, we expect that this work could be accomplished relatively quickly. The CPC is also happy to assist the agency in any way that it can in order to expedite the sharing of this information.

With regard to implementing this suggestion, we have heard that the agency is concerned that Good Guidance Practices (“GGPs”) apply to sharing this information on its website. We would like to take this opportunity to address that concern.

GGPs include the agency’s policies and procedures for developing, issuing, and using guidance documents. Among other things, GGPs provide for public input and participation in the development of “guidance documents.” The GGP regulation defines a “guidance document” as “documents prepared for FDA staff, applicants/sponsors, and the public that describe the agency’s interpretation of or policy on a regulatory issue.”⁴ The GGP regulation also provides that guidance documents do not include:

Documents relating to internal FDA procedures, agency reports, general information documents provided to consumers or health professionals, speeches, journal articles and editorials, media interviews, press materials, warning letters, memoranda of understanding, or other communications directed to individual persons or firms.⁵

GGPs must be followed “whenever regulatory expectations that are not readily apparent from the statute or regulations are first communicated to a broad public audience.”⁶

³ See II.B., regarding Advisory Opinions.

⁴ 21 C.F.R. § 10.115(b)(1).

⁵ § 10.115(b)(3) (emphasis added).

⁶ § 10.115(e).

The information that we are suggesting OCP share includes things like summaries of past decisions, warning letters, and meeting minutes. These communications were directed to individual combination product manufacturers and address the application of cGMP regulations to particular combination products. They fit squarely within communications to which GGPs do not apply -- “communications directed to individual persons or firms.”⁷ Because of this, GGPs do not apply to what we are suggesting FDA share on its website.

We acknowledge that we are suggesting that these one-on-one communications be shared with a broad audience; however, merely sharing that information does not mean that the communications are a “guidance document” that is governed by GGP. All over its website, FDA posts a variety of manufacturer-specific communications that are helpful to industry. For example, in addition to the jurisdiction-related information that we’ve already mentioned, FDA also posts selected EIRs and 483s, untitled letters, and warning letters. Manufacturers use this information to guide their own compliance decisions, to the benefit of FDA, industry, and ultimately, patients. GGPs are tremendously important, but they do not impede FDA sharing product-specific interpretations with industry.

We do want to mention, though, that on the OCP webpage where the jurisdiction-related information can be obtained, the agency provides: “It should be noted that jurisdictional updates report prior Agency decisions only and are not policy statements.” Though probably not required, we think that a “disclaimer” such as this would be appropriate for the similar cGMP information.

B. Field Force Consistency

During the May 4 meeting, the CPC and OCP discussed the variations among FDA’s field offices with regard to enforcement of cGMP regulations as applied to combination products. We’ve given this issue considerable thought and offer two key suggestions for addressing and improving the consistency and knowledge base of FDA’s field force with respect to the application of cGMP regulations to combination products.

1. Field Force Training and Coordination

First, because of the complexity of the different cGMP regulations and systems for drugs, biologics, and devices, inspecting combination product manufacturers for compliance with the cGMP regulations requires appropriately trained and experienced inspectors. To ensure that this occurs, the field force should first be alerted that an inspected firm manufactures combination products. We believe that a process should be developed to ensure that the field is alerted when an inspected product is a combination product, to the extent that such a process does not already exist.⁸

⁷ § 10.115(b)(3).

⁸ We understand that currently, the field force may be sent some portion of an NDA or other documentation for combination products where CDER is the lead Center, but that the field force may not

The CPC also believes that inspectors charged with responsibility for inspecting combination product manufacturers should be cross-trained on applicable regulations. The CPC further believes that in certain instances, inspection by a team of two or more inspectors with complementary knowledge, skills, and experiences may be appropriate.

However, while these suggestions are easy to state, their implementation issues can be decidedly more complex. Therefore, to facilitate their implementation, the CPC suggests that FDA develop procedures relating to the inspection and enforcement of cGMP regulations as applied to combination products. Below are the key issues the CPC believes FDA should address in these procedures:

- How the agency ensures that an inspector who inspects a combination product manufacturer has been appropriately trained.
- Criteria for determining whether a manufacturer's cGMP system can be adequately inspected by a single inspector who has been cross-trained or whether separate inspections of cGMP components are needed.
- How assignment of the lead center for regulating a combination product affects assignment of inspection personnel (e.g., Will "lead" inspection personnel vary depending on the assignment of a lead center?)
- How the agency ensures consistent treatment of similar combination products.

The CPC believes that FDA must give careful thought and consideration to these and related issues to ensure that cGMP regulations are appropriately applied throughout the combination product industry. In other areas of inspection and enforcement, FDA has internal procedures that agency staff follows to ensure efficient, fair, and thorough inspections of manufacturers.⁹ The combination product industry should be no different.

In addition to these questions, we would also encourage FDA's input on what role manufacturers can usefully play in developing appropriate solutions and in exchanging ideas related to training and development of personnel. Speaking for ourselves, the CPC would be happy to assist the OCP in formulating answers to these and other related questions that arise with respect to inspection and enforcement of cGMP regulations.

2. Process for Addressing Inconsistency Issues

Second, we believe that FDA should define a clear process for manufacturers to raise suspected instances of inconsistency in the application of cGMP 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

receive analogous information for combination products where CDRH is the lead Center (e.g., copies of the PMA).

⁹ See e.g., FDA, Office of Regulatory Affairs, Investigations Operations Manual (2006), Sections 5.4 (Food), 5.5 (Drugs), 5.6 (Devices), and 5.7 (Biologics); see also FDA, Office of Regulatory Affairs, Compliance Program Guidance Manual.

components are involved and informed of the outcome. In addition to enabling the agency and industry to identify and address inconsistency issues on a case-by-case basis, such a process would also enable FDA to identify areas of education and training for field office personnel and areas where industry needs more guidance on the application of cGMP regulations to combination products.

The CPC further suggests that the OCP consult with FDA's Office of the Ombudsman when developing this process, as the Ombudsman's Office is uniquely skilled in addressing issues of this type. Indeed, the Office's website describes its main function as being "to explore complaints and assist in resolving disputes between companies or individuals and agency offices" and further provides that the Office often addresses "claims of unfair or unequal treatment."¹⁰

C. Additional Guidance

As FDA is aware, combination product manufacturers have numerous questions about the application of cGMP regulations to combination products. Currently the agency is developing a proposed rule for cGMPs that apply to combination products, and the CPC wholeheartedly supports that effort. In the interim, though, combination product manufacturers must continue to rely on statements of FDA's current thinking on the application of cGMP regulations to combination products. This current thinking is represented by things such as agency statements, interpretation of existing regulations, and the "Draft Guidance for Industry and FDA: Current Good Manufacturing Practices for Combination Products". Although this is helpful, the CPC strongly believes that the agency should provide additional guidance on the application of the cGMP regulations. Without further guidance, waiting years for regulations to be promulgated puts an enormous strain on industry.

The members of the CPC have found that a "Frequently Asked Questions" format is extremely helpful in other areas of FDA regulation and believes that a "cGMP Regulation FAQ" would serve industry and FDA well. The CPC is currently drafting a FAQ document and will submit it to the agency soon as proposed guidance.

As a part of that guidance, the CPC also believes that the agency needs to provide more specific guidance on how cGMP regulations will be applied to particular types of combination products. More specifically, we see a critical need for guidance that uses specific case studies and examples to illustrate the agency's thinking. FDA has a tremendous opportunity to use its scientific expertise and experience to develop thoughtful and practical guidelines that will ensure consistent and predictable application of the regulations, and we urge the agency to maximize this potential. We will propose some case studies as part of the FAQ document we are developing.

III. Conclusion

¹⁰ FDA, Office of the Ombudsman, <http://www.fda.gov/oc/ombudsman/homepage.htm> and <http://www.fda.gov/oc/ombudsman/whencon.htm>.

The CPC appreciates the agency taking time to meet with us on May 4 and also appreciates the opportunity to provide these suggestions for improving the transparency of the application of CGMP regulations to combination products. As always, we are happy to assist in any way that we can.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Bradley Merrill Thompson", is centered within a light gray rectangular box.

Bradley Merrill Thompson,
On behalf of the Combination Products Coalition

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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.

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.

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 Reauthorization 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 (“IVDMIAAs”). 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 IVDMIAAs.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 GGP 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

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 GGP, 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 Reports*" 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:

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

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.

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,

A handwritten signature in black ink, appearing to read "Bradley Merrill Thompson". The signature is fluid and cursive, with the first name "Bradley" being the most prominent.

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

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

Developing Antimicrobial Drugs for Treatment

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

Products

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| 43. Comparability Protocols - Protein Drug Products and Biological Products - Chemistry, Manufacturing, and Controls Information | <i>Draft</i> | 9/3/2003 |
| 44. Current Good Manufacturing Practice for Medical Gases | <i>Draft</i> | 5/6/2003 |
| 45. Manufacturing, Processing, or Holding Active Pharmaceutical Ingredients | <i>Draft</i> | 4/17/1998 |
| 46. Powder Blends and Finished Dosage Units — Stratified In-Process Dosage Unit Sampling and Assessment | <i>Draft</i> | 11/2003 |

Revised Attachments

- | | | |
|--|--------------|----------|
| 47. Providing Regulatory Submissions in Electronic Format -General Considerations (Issued, Posted 10/22/2003) | <i>Draft</i> | 10/2003 |
| 48. Providing Regulatory Submissions in Electronic Format - Prescription Drug Advertising and Promotional Labeling | <i>Draft</i> | 1/2001 |
| 49. Labeling for Combined Oral Contraceptives | <i>Draft</i> | 3/2/2004 |
| 50. Labeling Guidance for OTC Topical Drug Products for the Treatment of Vaginal Yeast Infections (Vulvovaginal Candidiasis) | <i>Draft</i> | 6/1998 |
| 51. Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions | <i>Draft</i> | 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. <u>Integration of Study Results to Assess Concerns about Human Reproductive and Developmental Toxicities</u> (Issued , Posted 11/9/2001)	<i>Draft</i>	11/2001
54. <u>Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals</u>	<i>Draft</i>	5/2001
55. <u>Applications Covered by Section 505(b)(2)</u>	<i>Draft</i>	10/1999
56. <u>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</u>	<i>Draft</i>	12/1999
57. <u>Disclosure of Conflicts of Interest for Special Government Employees Participating in FDA Product Specific Advisory Committees</u>	<i>Draft</i>	2/14/2002
58. <u>Forms for Registration of Producers of Drugs and Listing of Drugs in Commercial Distribution</u>	<i>Draft</i>	5/14/2001
59. <u>Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions</u>	<i>Draft</i>	1/2004
60. <u>Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines</u>	<i>Draft</i>	3/9/2001
61. <u>Submitting Debarment Certification Statements</u>	<i>Draft</i>	10/2/98
62. <u>Submitting Marketing Applications According to the ICH/CTD Format: General Considerations</u>	<i>Draft</i>	9/5/2001
63. <u>The Use of Clinical Holds Following Clinical Investigator Misconduct</u>	<i>Draft</i>	4/2002
64. <u>Attachment G -- Draft Interim Guidance Document for Waivers of and Reductions in User Fees</u>	<i>Draft</i>	7/16/1993



1227 25th Street, NW
Washington, D.C. 20037-1156

June 20, 2011

VIA FIRST CLASS MAIL

Margaret Hamburg, M.D.
Commissioner
U.S. Food & Drug Administration
10903 New Hampshire Ave
Bldg WO1; Room 2228
Silver Spring, MD 20993-0002

Re: Transparency in Combination Products; Meeting Request

Dear Dr. Hamburg:

The Combination Products Coalition (“CPC”) would like to commend the Agency, and in particular the Office of Combination Products (“OCP”), on its attention to issues affecting combination products and how best to serve patient needs with respect to such products. We also like to commend the Agency generally for its efforts to increase transparency with regard to Agency regulation and enforcement. In this letter, we offer our thoughts on how the Agency’s Transparency Initiative should encompass combination products and how transparency in combination product regulation is necessary for forward progress on combination product policy development. This letter also discusses resource needs within the Agency with respect to 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 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.

1. THE TRANSPARENCY INITIATIVE & COMBINATION PRODUCTS

From a regulatory standpoint, combination products – products that involve the convergence of two or more different types of FDA-regulated articles (drugs, medical

devices, and biological products) – represent a regulated article that has its own unique regulatory scheme, just as pharmaceuticals, medical devices, and biological products do. From a patient health standpoint, combination products represent promising advances in patient care. Patients suffering from numerous types of serious diseases and conditions have already benefited from combination products, and many more innovative and beneficial combination products are currently being researched and developed. Industry estimates reflect this growth and development.

As regulated articles subject to their own regulatory framework and policy development, combination products should be included within Agency-wide initiatives, absent a specific and valid reason not to include them. In this regard, the Agency's Transparency Initiative should encompass combination products as articles regulated by the Agency.

Thus, although we are pleased the Agency has created the Transparency Task Force and proposed specific actions to increase transparency, we are concerned that the Task Force has overlooked combination products. Below we describe a few examples of where combination products are conspicuously absent from the Agency's recent publications on transparency.

For example, 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.¹ To take a more tactical 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.²

As another example, 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.³

We also support FDA generating and sharing information about the most common inspectional observations and practices.⁴ In this regard, FDA has recently created a public inspection classification database. However, this database does not seem to permit any

¹ See FDA Transparency Initiative: Improving Transparency to Regulated Industry 11-17 (January 2011).

² The product areas include: foods, cosmetics, dietary supplements, medical devices, radiological, animal veterinary, drugs, tobacco, and biologics.

³

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

⁴ FDA Transparency Initiative: Draft Proposals for Public Comment Regarding Disclosure Policies of the U.S. Food and Drug Administration (May 2010).

searches based on a product's status as a combination product, nor does it seem to provide information as to whether a given inspection involved combination products.⁵ Similarly, the Inspectional Observation summaries that were recently released do not denote when a product was a combination product or a constituent part of a combination product.⁶ This information would be extremely useful for combination product manufacturers in understanding how current regulatory requirements are applied to them.

Finally, we understand that there is an existing field within the Agency's internal databases indicating whether a submission is related to combination products. It would be helpful if the Agency included this field in public databases and allowed the public to search using this field. For instance, if the 510(k) clearances or PMAs could be filtered by whether the product was considered a combination product, combination product manufacturers would have additional insight into the nature of the filings required when seeking approval of a new combination product or when making changes to an existing product. In addition, including whether a product was combination product in the Adverse Event Reporting System data files or making this a searchable field in the MAUDE database would help combination product manufacturers determine who the responsible party may be with respect to post-market safety reporting. It also would be helpful to allow the public to search Warning Letters by whether the deficiencies related to combination products as this would provide additional insight into the Agency's interpretation of how the Drug, Device and Biological product regulations apply to combination products. This is not an exhaustive list of the databases we think would benefit from including this as a searchable field; however, we feel these should be prioritized.

We believe the Agency should ensure this information is provided for combination products just as it's 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. Below we describe the current status of key combination product policy issues and describe what information should be published to enhance transparency in the combination product industry.

2. Combination Product Policy Issues

Although combination products have not yet been included within the Agency's Transparency Initiative, the OCP and other parts of the Agency have participated in public dialogue on certain combination product issues and have done so in a transparent, fair, and balanced manner. The OCP also has been particularly successful in ensuring that combination product manufacturers get early, real-time access to FDA personnel to discuss development and manufacturing issues for these cutting-edge products. We commend the OCP on placing a priority on these types of informal communications, as gaining input on

⁵ <http://www.accessdata.fda.gov/scripts/inspsearch/>.

⁶ <http://www.fda.gov/ICECI/EnforcementActions/ucm250720.htm>.

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. However, as Agency data demonstrate, increases in the development and marketing of combination products have significantly impacted the Agency's workload, while the resources FDA has been able to devote to combination products have remained nearly static.

Therefore, despite the important success in preserving informal communications and maintaining regulatory responsibilities, important policy developments have had to take a back seat. Please consider the following examples:

- Good Manufacturing Practices (“GMPs”) for Combination Products – The Agency has publicly stated that the proposed rules on GMPs for combination products will not be finalized until the end of 2011. The Agency announced its intent to publish rules on combination product GMPs in early 2006. 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, and 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.⁷
- Post-Market Safety Reporting – As with GMPs, we understand that the Agency is predicting that the proposed rule on post-marketing safety reporting for combination products will not be finalized until the end of 2011. Although in the CPC's view the GMP regulations should have a higher level of priority, the post-market safety reporting requirements nevertheless deserve the Agency's focus and high prioritization. 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. As explained in the CPC's comments submitted on both rules, publishing

⁷ The Administrative Procedure Act (“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 (5 USC § 553). Although 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. We recognized that 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 (21 CFR § 10.40(g)).

these guidance documents, at least in draft form, *prior to* issuing the final rules is necessary to ensure stakeholders can comply with the final requirements within the effective date of the rules. We are concerned that the current resource limits may prevent the Agency from issuing these guidance documents in a timely manner.

- 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. Indeed, a few years ago, the CPC conducted an industry survey, which we have shared with the Agency, on the need for guidance in the combination product area. Post-market modification issues were among the topics industry rated highest as needing Agency 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 intent of stimulating Agency thinking. In our view, along with the proposed rules on GMPs and adverse event reporting, rules or guidance on the reporting of design and manufacturing changes to marketing applications should be one of the highest ranking priorities in terms of combination product policy development.
- 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. We are also not aware that a docket was established for this issue, so the public is unable to access any comments submitted.
- Registration and Listing – Currently there is no published guidance on registration and listing requirements for combination product manufacturers. We understand that OCP has been working on draft guidance for quite some time, and that this remains one of the most frequently asked questions of OCP.
- Clinical Study Requirements – Clinical trial requirements for combination products was 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 autoinjectors, human factors as part of Phase III studies, patient numbers 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*. We understand that OCP has developed an early draft of a guidance document.
- Autoinjector 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 autoinjector guidance that should clarify the numerous ambiguities in the draft guidance that was published a year and a half 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 autoinjector issues generally.

- Classification & Chemical Action – These are additional topics on which we understand the Agency has been developing a guidance document for quite some time; however, the Agency has not yet published a draft for comment.

To give patients access to innovative products, manufacturers need transparency, clarity, and regulatory predictability on these important policy development issues. Understanding the time and effort required to draft and finalize the above mentioned regulations and guidance, this letter outlines other methods by which the Agency can provide manufacturers the needed transparency while the regulations and guidance are being finalized.

3. NEEDED TRANSPARENCY IN COMBINATION PRODUCT ISSUES

As we all recognize, crafting new policies and regulations can be a painstaking process that takes a tremendous amount of time and effort on behalf of both the Agency and industry. While FDA is developing new regulations, though, manufacturers still need to comply with existing regulations. Combination product manufacturers specifically need tools to understand the application of existing regulations to combination products, while new regulations and guidance are developed. Below we summarize the information that should be posted.

Through its website, the OCP already shares a wealth of information with regard to the request for designation (“RFD”) process and jurisdictional decisions.⁸ We have found this information to be extremely helpful in determining which FDA Center is the “lead” for a particular product and for developing RFDs. However, the OCP has not posted recent decision letters; the most recent letter is dated January 17, 2007. In order to continue helping manufacturers determine which FDA Center is the “lead,” we request the OCP post redacted versions of recent jurisdictional decision letters soon after the letter is issued.

While a little less readily available, it would be helpful if the Agency were to also post summaries of previous Agency decisions and case studies addressing how GMP regulations apply to combination products. These current examples of Agency thinking will help manufactures ensure compliance and the availability of high quality products that health professionals and patients can use safely and reliably.

As described above, the Agency also should include combination products within the Agency’s Transparency Initiative. Information published under the Initiative would

⁸ See FDA, OCP, Jurisdictional Updates, *available at*: <http://www.fda.gov/oc/combination/updates.html>.

include the most common inspection observations and practices as they pertain to combination products. For example, the Agency should post redacted versions of FDA Form 483s, Warning Letters and Untitled Letters relating to compliance with regulations applicable to combination products in a timely fashion. Additionally, we also advocate for the posting of Agency presentations on combination products, guidance documents, and other Agency documents (e.g., manuals).

In summary, the CPC requests that the Agency publish the following information with regard to combination products:

- Jurisdictional Decision Letters;
- Form FDA 483s relating to inspections of combination products;
- Warning and Untitled letters relating to compliance with requirements applicable to combination products;
- Presentations by OCP employees and Center jurisdictional officers to external audiences at events sponsored by, or co-sponsored by, the Agency;
- Pertinent Guidance Documents and other FDA documents, e.g., manual updates;
- Summaries of previous Agency decisions addressing how GMP regulations apply to combination products; and
- Case studies and examples on how GMP regulations are applied to particular types of combination products

Generally speaking, this information should be readily accessible to FDA for sharing. Although in some cases FDA would need to draft summaries and redact information, we expect that this work could be accomplished relatively quickly.

Additionally, to facilitate the publication of some of this information, FDA may want to consider including a check box or some other way to designate whether a submission involves a combination product.

With regard to implementing these suggestions, we have heard that the Agency is concerned that Good Guidance Practices (“GGPs”) apply to sharing this information on its website. We would like to take this opportunity to address that concern.

GGPs include the Agency’s policies and procedures for developing, issuing, and using guidance documents. Among other things, GGPs provide for public input and participation in the development of “guidance documents.” The GGP regulation defines a “guidance document” as “documents prepared for FDA staff, applicants/sponsors, and the public that describe the Agency’s interpretation of or policy on a regulatory issue.”⁹ The GGP regulation also provides that guidance documents do not include:

Documents relating to internal FDA procedures, agency reports, general information documents provided to

⁹ 21 C.F.R. § 10.115(b)(1).

consumers or health professionals, speeches, journal articles and editorials, media interviews, press materials, warning letters, memoranda of understanding, or *other communications directed to individual persons or firms.*¹⁰

GMPs must be followed “whenever regulatory expectations that are not readily apparent from the statute or regulations are first communicated to a broad public audience.”¹¹

The information that we are suggesting OCP share includes things like summaries of past decisions, warning letters, and meeting minutes. These communications were directed to individual combination product manufacturers and address the application of GMP regulations to particular combination products. They fit squarely within communications to which GMPs do not apply -- “communications directed to individual persons or firms.”¹² Because of this, GMPs do not apply to what we are suggesting FDA share on its website.

We acknowledge that we are suggesting that these one-on-one communications be shared with a broad audience; however, merely sharing that information does not mean that the communications are a “guidance document” that is governed by GMP. All over its website, FDA posts a variety of manufacturer-specific communications that are helpful to industry. For example, in addition to the jurisdiction-related information that we’ve already mentioned, FDA also posts selected EIRs and 483s, untitled letters, and warning letters. Manufacturers use this information to guide their own compliance decisions, to the benefit of FDA, industry, and ultimately, patients. GMPs are tremendously important, but they do not impede FDA sharing product-specific interpretations with industry.

We do want to mention, though, that on the OCP webpage where the jurisdiction-related information can be obtained, the Agency provides: “It should be noted that jurisdictional updates report prior Agency decisions only and are not policy statements.” Though probably not required, we think that a “disclaimer” such as this would be appropriate for the similar cGMP information.

4. COMBINATION PRODUCT RESOURCES WITHIN THE CENTERS

We again, commend the Agency’s participation in public dialogue on combination product issues, which it has done in a transparent, fair, and balanced manner. However, as described above, increases in the development and marketing of combination products, which can only be expected to continue, have significantly impacted the Agency’s workload, while the resources FDA has been able to devote to combination products have remained nearly static. As a consequence of this continued growth, the Agency has had to focus primarily on its regulatory responsibilities with respect to combination products, which the Agency has executed in a timely and efficient manner.

¹⁰ § 10.115(b)(3) (emphasis added).

¹¹ § 10.115(e).

¹² § 10.115(b)(3).

We are concerned that, without additional Agency resources focused on combination products, the ever-increasing demands will impede combination product innovation and development, as well as the valuable interaction and dialogue among the OCP, the Centers, and regulated industry on both marketing submissions and post-market compliance issues. To preserve their value, these types of communications should remain informal and a co-equal priority with other agency activities.

Further, a key challenge with developing combination product policy is that it is intertwined with regulatory issues pertaining to drugs, medical devices, and biological products. Therefore, in addition to the OCP's driving force, significant participation and input is required from CDER, CDRH, CBER, and the Office of the Chief Counsel. This input on policy issues is in addition to the frequent input the Centers must give on applications and routine, specific questions about jurisdictional issues and specific products.

Not surprisingly, then, the Centers also have felt the strain of the increases in the number of combination product submissions and of the huge amount of policy-related work that remains to be done in the combination product area. Our perception is that the combination product resources within the Centers have become particularly strained in their abilities to provide necessary input and sign-off on combination product policy, thereby impeding advancement of the policy development. We understand that a particular need exists within the Centers for personnel dedicated to combination product issues, and in particular combination product policy development.

To support the Agency's Transparency Initiative, including the development of the above-identified policy priorities and the preservation of the valuable informal Agency-industry dialogue, the CPC recommends that the Agency review the Agency's prioritization of and resources allocated for combination product issues and consider ways in which the Agency could support the advancement of combination product policy development without jeopardizing the current level of informal discussions with the industry. **At minimum, we recommend that the Office of the Commissioner add at least one FTE in each Center who is formally tasked with ensuring the advancement of regulatory policy concerning combination products.**

5. MEETING REQUEST

We would like to schedule a meeting with you to discuss these important issues impacting combination products. To arrange a time when we could meet, please contact me at: bthompson@ebglaw.com or (202) 861-1817.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Bradley Merrill Thompson". The signature is fluid and cursive, with the first name "Bradley" being the most prominent.

Bradley Merrill Thompson,
On behalf of the Combination Products Coalition

Enclosure

cc:

Thinh X. Nguyen
Director, Office of Combination Products

Jill Warner
Acting Associate Commissioner for Special Medical Programs

Barr Weiner
Associate Director for Policy and Product Classification Officer, Office of Combination
Products

Lisa Dwyer
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Members of the Transparency Task Force