

Combination Products: Proposed Policies to Enhance the FDA Regulatory Process

I. Introduction

Combination products increasingly include state-of-the-art, innovative technologies with great potential to advance patient care. Combining different regulated product types, however, triggers a panoply of issues with which the Food and Drug Administration ("FDA"), pharmaceutical, biologics and medical device manufacturers, and other stakeholders have struggled through the years. Since 1991, FDA has worked toward resolving a number of these issues, and has made some inroads in assignment of jurisdiction for combination products.¹ We are encouraged by FDA's preliminary efforts, and look forward to further improvements in the regulatory process for combination products.

Notwithstanding FDA's efforts to date, significant issues remain. A group of about 20 companies, most of which are leading pharmaceutical, biologics and medical device manufacturers with substantial experience in the combination products arena (the "Coalition") have engaged in an ongoing discussion of these issues. In addition, the Coalition has solicited comments through mailings to members of the drug delivery industry and other manufacturers of combination products. Through this process, the Coalition identified five key opportunities for improvement:

- **Labeling**—FDA needs to adopt a guidance for combination product labeling that: (a) Clarifies cross-labeling requirements for virtual combination products; (b) adopts the most appropriate reviewing time for labeling changes; and (c) clarifies the format and content requirements for labeling of combination products, particularly when a single integrated label is required.
- **Modification of approved combination products**—FDA should clarify, in a guidance, the regulatory pathway for changes to components of approved combination products.
- **Adverse Incident Reporting**—FDA should in the short-term develop guidance that clarifies how the reporting requirements contained in the rules for drugs, devices and biologics apply to combination products, for both investigational and post-approval combinations. Ideally, in

¹ In the first half of 2003, the OCP issued nine (9) assignments. Of those assignments, seven were of drug-device combinations, three of which were assigned to the Center for Drug Evaluation and Research ("CDER"), and four of which were assigned to the Center for Devices and Radiological Health ("CDRH"). The remaining two combinations involved biologics and were assigned to the Center for Biologics Evaluation and Research ("CBER") (1- drug-biologic combination, and 1- device biologic combination.). All assignments were issued within the mandated time frames, and only one company requested reconsideration of the assignment.

the long term, FDA should move toward a single system for the reporting of adverse incidents for all products to a single FDA office.

- **Quality systems**—FDA should clarify the applicability of the various good manufacturing and quality system requirements.
- **Clarification of Roles of Office of Combination Products ("OCP") and Centers.** FDA should clarify the role of OCP, and the roles of the individual centers in the process.

As you will see, the majority of recommendations in this document focus on clarifications to the existing processes, as well as the applicable rules. Our goal through development of these policy recommendations was not to add bureaucracy to the system, but to simplify the regulatory paradigm for combination products as much as possible. Clearly, not all combination products are the same. Indeed, they represent perhaps the greatest level of diversity with which FDA has ever been faced. For that reason, although the regulatory paradigm must remain relatively simple in application, it must have tremendous flexibility; a "one size fits all" approach simply will not work.

The regulatory paradigm that ultimately governs combination products must also fit within FDA's existing statutory authority. Our goal is not to expand on Congress' mandates regarding combination products, but to clarify through guidance and regulation FDA governance of drug, device and biologics combinations under those mandates. Specifically, we recognize that Congress granted FDA the authority to determine whether a combination product has the primary mode of action of a drug, biologic or device, and on that basis to assign an agency center to have primary jurisdiction over pre-market review of that combination.² In addition, Congress charged FDA with ensuring consistency and appropriateness of post-market regulation of like products. However, Congress did not grant FDA the authority to create a new regulatory scheme specific to combination products. Rather, FDA has the authority to draw upon the existing scheme and to apply the most appropriate statutes and regulations depending on the nature of the combination product.

That said, we urge FDA to work with the Coalition and interested stakeholders to flesh out solutions that can be implemented in the identified areas, within the scope of existing statutory authority. To that end, the Coalition seeks to engage in an ongoing constructive dialogue with the FDA Office of Combination Products ("OCP") as well as appropriate management members from the FDA centers for drugs and devices about the issues and proposals provided in this document. We recognize that some of these issues and proposals may generate questions, and that finding appropriate solutions requires dialogue. Therefore, the Coalition respectfully requests that the OCP and management members from each of the centers meet with members of the Coalition in the near future to discuss these comments in more detail. Through this interaction, the FDA can be assured of receiving the specific industry examples and

² See 21 USC 353(g).

experiences that will help FDA produce meaningful guidance or regulations on the important topics raised here.

With that in mind, we present the following proposal for FDA's consideration.

II. Proposed Policy Enhancements

Building on FDA's own innovative efforts to refine and refocus the combination products approval process and construct a special office to address combination products issues, the Medical Device User Fee Modernization Act ("MDUFMA") mandated an OCP to oversee assignment, review and post-market regulation of combination products. More specifically, the OCP is charged with three statutory duties: (1) Prompt assignment of combination products to the agency center with primary jurisdiction for the premarket review of the product; (2) ensuring the timely and effective premarket review of combination products; and (3) ensuring the consistency and appropriateness of postmarket regulation of like products subject to the same statutory requirements to the extent permitted by law.³ The OCP also is responsible for resolving disputes regarding the timeliness of premarket reviews.

As already noted, while some improvements have been made to the process under coordination by the OCP, challenges remain. Before exploring the opportunities for improvement, though, we need to set the framework for the discussion.

A. Types of Combination Products

In assessing the current process, it became apparent that the significance and complexity of issues may depend on the type of combination product involved. Indeed, a combination product involving two clearly separate components may give rise to very different issues than a combination product that is manufactured as a unit. For that reason, they need to be treated differently. With that in mind, we propose to approach the regulation of combination products in terms of three identifiable types, each of which has its own issues. These categories, which derive from the regulations defining combination products, include:⁴

- Integral combination products: Two or more regulated products combined as an inseparable unit. Examples: Drug-eluting stents, pre-filled syringes.
- Kits: Combination products comprised of two or more regulated products packaged together, but with components that can be separated easily. Examples: Antibacterial scrub with catheter; drug additive with IV kit.

³ See 21 U.S.C. 353(g); *see also* U.S. Food and Drug Administration, Overview of the Office of Combination Products (visited September 12, 2003) <<http://www.fda.gov/oc/combination/overview.html>>(explaining the role of the Office of Combination Products).

⁴ See 21 C.F.R. 3.2(e) (identifying four types of combination products). For the sake of simplicity, we do not discuss combinations in which each of the components is investigational.

- Virtual combination products: Products that, in concept and labeling, must be used together to achieve the intended use, indication or effect, but are not packaged together.⁵
Example: Herceptin and Herceptin Test.

In addition, because of the unique issues that arise with the second, third, or more iteration of a product, we propose to keep in mind the stage of the combination product when considering enhancements to the existing process.

With that background in mind, we propose the following policies to enhance the combination products' regulatory environment.

B. Proposed Enhancements

1. Labeling

Labeling for combination products creates a tremendous challenge for FDA and manufacturers. The current regulatory scheme, which regulates the labeling of the various combination product *components*, does not regulate or provide guidance for the structure and content of labeling for combination products as a *unit*. Consequently, a number of issues can arise. The nature and complexity of these issues depends, in part, on the type of combination product involved.

For an integral combination product for which a single integrated label is required, clarification is needed on the specific content and format of that label and labeling. For an integral drug-biologic combination product, the format and content of the label and labeling may seem reasonably straightforward since the label and labeling of both drugs and biologics generally follow the same format and content. However, in the absence of guidance or regulation the format and content of the label and labeling remains undefined for an integral drug-device or biologic-device combination product. This could result in a label with so much information it becomes difficult for users to read, or a label focused on one component of the combination product to the exclusion of the other. Presumably, how this issue is resolved would be influenced by the approval mechanism for the combination product. For example, if an

⁵ By definition, if a product is not intended for use with another individually specified product, it is not a combination product. See Final Rule, Assignment of Agency Component for Review of Premarket Applications, 68 Fed. Reg. 37075, 37075. The term "combination product" is more specifically defined by regulation to include (1) a product comprised of two or more regulated components; (2) two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products; (3) a drug, device or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed; and (4) any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device or biological product where both are required to achieve the intended use, indication, or effect. 21 CFR 3.2(e).

integral combination product is approved under a drug or device application, the format and content of the label and labeling of the integral combination product might be driven by the label and labeling regulations related to that particular approval mechanism. This format and content might then be augmented with information related to the other component. Regardless, the specifics need to be clarified.

For a kit combination product, the individual kit components have their own labels and labeling. Nonetheless, the overall label and labeling for the kit as a co-packaged unit needs to be defined. For instance, it is not clear how co-packaged medical devices and drugs – such as drug delivery devices plus drug, or surgical instruments plus drug(s) -- will be labeled. In addition, it is not clear what labels and labeling might be required for kit combination products when the components are separately cleared or approved and a separate kit approval is not required.

Although virtual combination products are labeled according to the label and labeling regulations for each particular product type, issues still need to be addressed. For instance, the specific content of labeling for virtual combination products remains unclear, as does the appropriate process for ensuring that labeling remains up-to-date, accurate, and mutually conforming.

Finally, changes in labeling of all types of combination products can cause unnecessary delays in securing product approval for modifications to the product, particularly if two or more centers are involved in label negotiations and approval.

- For example, one manufacturer sought to add the name of a 510(k) cleared reusable drug delivery system to its drug label. CDER, however, believed that simply adding information about the cleared device to the approved drug label required additional prior approval. Consequently, CDER requested device performance data and reviewed this information under the time frames and guidelines for drug review (for a prior approval 314.70(b) supplement). The labeling change took years, despite the fact it was an approved drug used with a cleared device.
- Similarly, a manufacturer sought to have information and instructions for use for a 510(k)-cleared insulin pump added to the label for one of its approved insulin products. CDER requested substantial additional data, some about the drug stability in the device, but also about the device performance characteristics. This additional information required submission of a prior approval 314.70(b) supplement.
- One manufacturer purchased boxes of 500 alcohol swabs from another company, and put one swab in each of its kits. The Drug Facts labeling for the alcohol swabs was included on the outer box containing the 500 swabs, but not on the individual swabs. Consequently, the kit manufacturer faced a dilemma on labeling of the kits with the required Drug Facts language. This raised issues of product and labeling integrity for the companies.
- A manufacturer of a blood culture procedural tray was required to comply with both *in vitro* diagnostic ("IVD") device requirements, and the OTC Drug Facts labeling. To

meet the size requirements for the Drug Facts, the company had to compress the IVD labeling, and rely on the small size exemption to omit information that otherwise might be required. The pathway to compliance was rough and un-charted.

- Also, unlike typical drug package labeling, the outer package of a drug-eluting stent neglected to include valuable drug dose information. To obtain the drug dose associated with that particular stent, a healthcare provider would have to cross-reference the catalog or part number of the stent with the drug dose. That information is accessible on the Internet – but not easily accessible to a cardiologist (physician) preparing to implant a drug-eluting stent into a particular patient.

Given these challenges, we propose that the labeling of combination products be enhanced in three ways: (a) Clarify cross-labeling requirements for virtual combination products; (b) adopt the most appropriate reviewing time for labeling changes; and (c) clarify the format and content requirements for labeling of combination products, particularly if a common label is required. We discuss each of these areas below.

a. Cross-labeling

As described above, under the current process, the rules regarding cross-labeling of virtual combination products can cause confusion and unnecessary delays. The lead centers are not always clear on the data required for cross-labeling (particularly with drug-device combinations) and they are not always clear *when* cross-labeling is required. This latter problem cuts to the very heart of the issue.

To enhance the process and eliminate the confusion regarding when cross-labeling should occur, we propose to require cross labeling of products under two circumstances:

- When, in a package insert or instructions for use, one product refers to another product *specifically by brand*. For instance, if a reusable syringe labeling says it is designed for use with a specific branded drug, the syringe would need to be cross-labeled accordingly; and
 - Only if the two *components* are designed to work together do the regulations require, and does it make sense, that they be cross labeled as combination products.⁶ Without limiting the application of that rule to references of a specific brand, a plethora of combination products would be created where indeed no combination is contemplated and the combination product rules provide no extra public health protection.
- A product cannot be used safely or effectively without identifying a branded product with which it must be used.

⁶ See 21 CFR 3.2(e) (defining combination products).

- For example, in the situation of general dose delivery systems where the drug is removed from its primary container closure and placed in a device for an extended period of time (such as infusion pump or needle free injection), there are some unique questions that can be raised. These questions should be answered fully in the product review process. There are many formulations of drugs that might be used in these systems but we suggest that not all the safety and efficacy questions have been addressed for these formulations. Does the delivery system create a difference in how the drug is administered? A drug product with proven efficacy through discrete subcutaneous injections may not have the same efficacy when the drug is administered through continuous subcutaneous infusion or when it is forced through the skin (i.e., needle free injection). Has the drug formulation stability been demonstrated over the time that the drug could reside in the delivery system and at the temperature or other conditions that it might be exposed to? Finally, can the biocompatibility testing of the device materials be applied to the use of the drug product formulation in those materials? Could the drug elute different substances from the device materials that have not been proven to be safe in the biocompatibility testing? These types of devices should not be considered general delivery devices and cross labeling with a specific branded drug should be required.

b. Reviewing Time

To avoid duplication of effort and to ensure timely review of labeling, redundant review should be avoided. Under the current process, it is not unusual for a second center to conduct what amounts to a second review of data already reviewed in the process of clearing or approving a drug, device, or biologic. While in some cases consultation between centers may make sense, a second review sometimes ignores the conclusion of the initial reviewing center – which typically has the greater expertise regarding that component of the product. For instance, as discussed above, if CDRH clears a device under the 510(k) process, that 510(k) review should be accepted by a CDER reviewer considering whether the device instructions for use can be included in a label for a combination product. The data are the same. The conclusion should be the same. With that in mind, we offer the following specific recommendations:

- When a second review is unnecessary because the issues have already been examined in a prior review, the labeling changes, in some instances, may merely be reported (for example, in the annual report for the drug).
 - For instance, one manufacturer sought to add to its drug labels information about a 510(k)-cleared drug delivery device to be used with the already-approved drug cartridges. However, the CDER reviewer asked to review the exact same dose accuracy testing data reviewed by CDRH in the 510(k) clearance process – data based on

testing with saline cartridges. CDER took years to review this data, despite the prior review and clearance by CDRH.

- When there are changes to the labeling realistically related only to one component that need to be reviewed, the review should be conducted under the applicable review process for that component and according to those time frames regardless of which center is the lead center. For example, a label change to the device component of a combination product that is approved by CDER should not have to follow the lengthy drug supplement review time. Instead, a device review time frame is more appropriate in this case. (That would still allow for consultation between centers to ensure that there are not issues involving the other component/center that have gone unnoticed.) For example:
 - If, based on customer feedback, a manufacturer seeks to improve the instructions for use for an integral combination product, such as a pen injector approved by CDER, the review of this type of change should not be subject to a lengthy drug supplement reviewing time.

Finally, we propose that the OCP take a stronger role in facilitating and monitoring the labeling review process. In fact, we believe that it is the OCP's statutory duty to do so. Congress gave OCP authority to ensure the timely and effective premarket review of combination products. Labeling is crucial to that review. Moreover, effective labeling is key to the effective use of the combination. OCP can assist by ensuring that the best thoughts of the centers are united in one label, and that labeling reflects the true efficacy and safety of the combination product.

c. Format and Content of Labeling

To ensure that labeling is consistent, adequate, and effective, we propose that FDA develop guidance describing the format and content required for combination product labels and labeling – including any package insert and other instructions for use – for combination products for which a common label is required. The regulations clearly define what must be included in labeling for prescription drug products and biologics.⁷ Similarly, the regulations specify the instructions for use that must accompany medical devices.⁸ However, it is unclear how these regulations are to be applied to combination products. For this reason, we encourage the OCP to develop guidance for the format and content of labeling for combination products. In so doing, OCP should move toward harmonizing its labeling requirements with those of regulatory authorities outside of the United States.

⁷ 21 CFR Part 201.

⁸ 21 CFR Parts 801, 809.

2. Modification of Approved Combination Products

Later iterations of combination products can raise significant, different jurisdictional issues. An issue is likely to arise most often with modification of a device component of a drug/device or biologic/device combination under the jurisdiction of CDER. With such combinations, the modification of the drug component would be handled under the drug rules. Although intuitively the device component should be handled under the device rules, that is not always the case. FDA currently might require a modification to the device components also to be reviewed under the drug rules. That can dramatically change the process required. For example, while most drug-type changes might require a supplemental NDA of some sort, new 510(k)s are not required for many types of changes to a 510(k)-cleared device. A drug-type review for a device change can significantly affect the implementation of the change.

In addition, the drug regulations require supplements (sometimes with associated fees) for changes for which 510(k) device requirements do not even require notification, much less FDA review. Therefore, there may be differences in the costs of complying with one set of regulations or another.

Moreover, application of device rules to such changes in device components of combination products is not always clear. In fact, the fundamental guidance document for 510(k) modifications is not intended to apply to combination products.⁹ Consequently, manufacturers of drug/device and biologics/device combinations are left without clear guidelines on the circumstances in which they can document changes to the device component of the product, rather than seek clearance. To complicate matters, how modifications are treated may depend on whether the products are packaged together as a kit, or clearly separate.

- For instance, one manufacturer modifying a pre-filled syringe system made a change to the device component of the combination product that would have been considered minor under the 510(k) guidance applicable to medical devices. However, the change was treated as a major change because the combination product was under the jurisdiction of CDER.
- A manufacturer considered the addition of a new assembly line for its pre-filled pen injector. The new line would manufacture the device component and then combine the device component and drug component (in its approved container closure) in the final combination product. Since the modification involved the manufacture of the device component, the 510(k) decision tree was used as a guide, and it was determined that a new 510(k) would not be necessary if the product only contained a device. When the manufacturer suggested that the new operation be included in the NDA annual report, the CDER review branch disagreed, stating that the device component was secondary

⁹ U.S. Food and Drug Administration, Deciding When to Submit a 510(k) for a Change to an Existing Device 4 (1997).

packaging and a "change being effected" supplement under 21 CFR 314.70(c) was necessary. If the manufacturer had followed the quality requirements for drug product secondary packaging, detailed design control and validation activities could have been ignored.

To clarify the most appropriate handling of such modifications we propose the following:

a. Device components cleared by CDRH

For changes to device components in virtual combination products and “kits” where the device component is cleared by CDRH, we propose that FDA continue to use *Deciding When to Submit a 510(k) for a Change to an Existing Device* guidance to guide the need for a submission.

b. Device components approved by CDER

For integral and virtual combination products approved by CDER, we propose the development of a regulatory scheme, or guidance, that uses a top-level decision-tree, flow chart or matrix to identify appropriate regulatory handling of the modification depending on the specific combination product scenario. This decision tree should incorporate a risk-based model that considers the safety and effectiveness of the finished product. In other words, where does the risk reside with respect to the particular modification – in the drug component, or the device component? For instance:

- A pre-filled drug delivery system likely would fall within CDER’s purview. Nonetheless, a post-approval modification of the device component in the next generation should be subject to the 510(k) modification guidance, and any submission formatted and reviewed as a 510(k). CDER would retain jurisdiction, but CDRH would then act as a consulting center on the modification.
- In contrast, where a modification does not require a 510(k) under this new guidance, the modification would be filed in an annual report under 21 CFR 314.70(d), provided the modification falls within the scope of the original NDA commitments.

With each of these scenarios, the application required should be the least burdensome application appropriate. In addition, the time frame for review should be those of the 510(k) submissions. This would keep device component changes consistent with their medical device counterparts currently subject to the 510(k) guidance, providing greater consistency in the regulatory scheme. This would also build efficiency and effectiveness into the process, and comport with the required least burdensome approach.¹⁰

¹⁰ 21 U.S.C. 360c(a)(3)(D)(ii); 21 U.S.C. 360c(i)(1)(D).

3. Adverse Incident Reporting

The consistent regulation of combination products is complicated by a lack of regulatory guidance specific to reporting adverse incidents related to combination products. This creates significant problems for reporting of investigational adverse events and adverse device effects, as well as adverse drug experiences, adverse device experiences, and MDR reporting, which have different reporting thresholds and timetables. The problem is particularly acute when expedited reporting is involved. For instance:

- The regulations at 21 CFR § 314.80 require expedited reporting of serious adverse drug experiences within 15 calendar days, but only if unexpected.
- In contrast, the device regulations require reporting of an adverse device experience within 30 days if the device may have caused or contributed to a death or serious injury, or has malfunctioned and would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.¹¹
- In addition, MDR reportable events that necessitate remedial action to prevent an unreasonable risk of substantial harm must be reported in 5 workdays.

These different reporting thresholds and time periods, as well as uncertainty on which center should receive the report, or whether dual reporting is required, can cause confusion among manufacturers trying to comply. This leads to inconsistency in compliance and, in some cases, duplication in reporting or over-reporting. Similarly that confusion can lead to inconsistency in enforcement. Moreover, the choice of what regulations apply may differ depending on which center takes the lead in the review of the product application; often these obligations are not clearly spelled out at the time of approval.

This conflict among the regulatory schemes governing the components of the combination products may play out in a number of different ways. For instance, when a device or drug is involved in a patient incident, the physician involved in the incident may not be sure which component of the combination product actually caused the event or incident – whether it was a drug reaction or an injury caused by a device incident or malfunction. Consequently, the manufacturer's report may go to the wrong place, be reported on the wrong time frame, or not be reported at all.

- For example, a reusable insulin pen-injector cleared by CDRH under a 510(k) and a disposable pre-filled insulin pen-injector approved by CDER under an NDA may be subject to different reporting obligations. If serious hypoglycemia were to occur due to a malfunction of the device, the centers could adopt two interpretations of expedited reporting requirements: (1) CDER, which has primary jurisdiction in the case of the pre-filled disposable pen, might conclude under the drug regulations that, because

¹¹ See 21 CFR 803.50; 805.53.

hypoglycemia is an expected adverse event with insulin therapy, the event is not reportable; while (2) CDRH, which has primary jurisdiction in the case of the reusable pen, might conclude under the device regulations that the expectancy of the event is irrelevant and therefore, the malfunction is reportable.

To alleviate these problems, we propose both short-term and long-term enhancements to the reporting scheme applicable to combination products. The purpose of these enhancements is two-fold: (1) To clarify the reporting obligations for combination products and thereby ensure regulatory compliance; and (2) to ensure patient safety through appropriate reporting of safety issues. In accomplishing these purposes, we seek greater simplicity in the reporting system, and would like to work with FDA toward that end.

a. Short-term: Guidance

In the short-term, we propose that the OCP develop guidance for the centers and manufacturers that clarifies how the reporting requirements contained in the rules for drugs, devices and biologics apply to combination products, for both investigational and post-approval combinations. This guidance should provide recommendations based on the type of combination product at issue, without regard to the reviewing center. It should set forth required reporting for various types of combination products, and timelines for general and expedited reporting.

With respect to content of the Guidance, we propose that the OCP apply the existing rules for drugs, devices and biologics as appropriate based on the risk involved and the type of combination product, regardless of which center takes the lead. For example, the rule on device malfunctions generally should apply to all drug/device combination products, regardless of which center takes the lead. Similarly, if the drug component is clearly at issue, then the drug rules should apply, even if CDRH is the lead center. A top level risk-based decision tree or flow chart included in the guidance would be an effective tool in helping centers and manufacturers determine what reporting obligations apply under what circumstances. In addition, the guidance should include examples of some of the more difficult combinations, and what reporting obligations should apply. Such examples might include:

- In the case of a virtual combination involving an *in vitro* diagnostic – drug combination, it may be difficult to tell if an adverse event is due to the drug, or to a misdiagnosis from the IVD.

b. Long-term: Single Reporting Scheme

In the longer term (and this would require a statutory change), we propose that Congress and FDA adopt a single system of reporting that focuses on combination products as a unit and does not make needless distinctions between drugs, devices, and biologics in determining what applies. This system should be devised with consideration for global harmonized reporting mechanisms already in place. Such an improvement in the reporting scheme is likely to lead to more and better reports by manufacturers, who are often confused by the existing reporting requirements of drugs versus devices, and commercially-available product versus investigational-use only product. More and better reporting can only lead to improved patient safety. This long-term approach obviously would require development of a regulatory

scheme specific to combination products, particularly integral combination products and kits, and would need to address the unique issues presented by innovative pairings involving biologics. Indeed, it probably would replace the separate individual reporting systems for drugs, devices and biologics. To that end, it would mandate reporting to a single office within FDA.

In addition, in developing the new system, we encourage Congress and FDA to work toward harmonization of its reporting system with approaches adopted by the international community. Although the regulatory status of combination products currently varies from country to country, the need for reporting of safety issues is a common thread. Moreover, the international community, through the Global Harmonization Task Force, is working toward harmonization of safety reporting. While such harmonization may take time, it behooves FDA to keep an eye on international developments, and work toward harmonization with international standards and requirements.

4. Quality Systems

As FDA heard at the Public Hearing on FDA Regulation of Combination Products held in November 2002, it is difficult and confusing to apply two different quality systems to the same product, but that can happen in the realm of combination products. When the combination product involves a drug/device virtual combination or a kit in which the components are developed and manufactured separately, application of the quality system regulations (“QSRs”) to the device component and good manufacturing practices (“GMPs”) to the drug component makes sense, and may be accomplished without overlap or confusion. Consequently, the separate regulatory schemes applicable to those separate components should continue to be applied. However, when the combination product is an integral combination product developed and/or manufactured as a unit in one facility, or a virtual combination product where the device component is approved by CDER, the application of QSRs and/or GMPs becomes unclear. This can lead to inconsistent regulation of like products, which, in turn, leads to inconsistency in manufacturer compliance, as well as inconsistency in inspection and enforcement. This inconsistency may extend from company to company, center to center, or region to region. While some differences between regulation of different technologies is, in all likelihood, warranted, the concern here is for consistency of regulation among *similar* technologies. Simply put, if the players do not know which rules to abide by, they may well be applying different rules to the same product.

The problem stems from the different intent of at least two regulatory schemes.¹² The drug GMP scheme was developed to ensure the purity, potency and lack of adulteration of drug products. In contrast, the QSR scheme is concerned with ensuring that devices are designed in a way that meets customer and regulatory requirements and manufactured in a way in which they meet specifications. From these different intentions derive two distinct systems.

¹² We recognize that regulations setting forth good tissue practices are pending. This additional regulatory scheme could further complicate the picture.

For instance, QSRs focus on design control, which includes a documented development plan, design review, defined phases of development that do not necessarily compare with those of drug development, a defined technology transfer process, and a design history file. None of these elements are mandated under GMPs. In addition, QSR includes requirements for defined corrective and preventive action systems, which differ from the GMP requirements to investigate product failures and deviations. QSR also contains specific requirements on management oversight that are not contained in the GMPs. Moreover, the quality manual requirement of QSR is absent from GMPs. Finally, while risk management may be a familiar concept within the drug industry, it is not mandated by GMPs as it is by QSRs. Consequently, FDA and manufacturers face a conundrum when determining how to apply the systems to certain combination products.

Interestingly, the issues raised by the QSR versus GMP issue have led manufacturers to adopt new strategies on the front end of the process that impact later issues. When a manufacturer submits a Request for Designation ("RFD"), that manufacturer has an opportunity to propose which center should take the lead. That may be motivated by the desire to have either a drug or device designation imposed on the particular combination product at hand. The center designated as lead center can dictate what applies – QSRs or GMPs.

However, there remain significant concerns regarding which rules apply. Consequently, we propose that the OCP take a two-step approach to developing appropriate guidance for integral combination products:

- First, we propose that the OCP, at the outset, set forth general principles regarding the controls on development and production of combination products. In developing these general principals, FDA should use the process for a level 1 guidance to ensure that they are well--vetted to manufacturers and other stakeholders.¹³
 - This guidance would recognize that each combination is different and that one regulatory solution will not necessarily fit all development and production scenarios.
 - With that in mind, the guidance should incorporate a risk-based model for deciding which regulations might apply for a particular combination product.
 - At the same time, this guidance should respect the separateness of the component parts and their relative quality systems, while clarifying what FDA expects from manufacturers.
 - Another goal in developing a solution to this issue ought to be minimizing complexity of the regulatory scheme wherever possible.

¹³ See 21 CFR 10.115(g)(1).

- Finally, a guidance should define when to use collaborative versus consultative review.
- Second, we propose that, based on these general principles, the OCP develop a further guidance that sets forth QSR and GMP requirements for combination products in greater specificity based on experience with inspecting combination product facilities. The guidance would be tailored to accommodate a variety of different combinations using a tiered approach. In that regard, the guidance would take a case study approach, cite examples of different types of combination products and situations, and specify what type of QSRs and/or GMPs would be required. It would also address inspections, including pre-approval inspections, for production facilities manufacturing combination products. Along with this guidance, FDA clearly would need to cross-train inspectors on the nature of combination product inspections, and the level and type of GMP and QSR-type requirements that would apply in any given scenario. In the alternative, FDA could send in two inspectors working as a team – one from CDRH and one from CDER.
- Finally, a procedure needs to be implemented to enable manufacturers to seek approval or "buy-in" from FDA on manufacturer's quality systems and GMP processes. This would ensure greater communication between industry and FDA, and result in greater compliance.

By setting forth general principles and adopting guidance for quality systems and GMP requirements applicable to combination products, the OCP will clarify for manufacturers the rules of the road. Questions may remain, however, which road should be followed with respect to a particular combination product. Therefore, it will be important for OCP to optimize the RFD phase by determining which regulatory path will be applicable to a combination product as early in the review process as possible. If the systems are harmonized and clarified, and expectations set forth and agreed upon early in the process, the OCP can expect greater compliance.

5. Clarification of Roles

A number of challenges arise within the current process because of the inherent need for collaboration or consultation between centers involved in review of a particular combination product. To address these challenges, we propose that the OCP truly become a functioning body and take a stronger and more visible role in the process -- a role that we believe is authorized by statute. In addition, we propose that the roles and relationships between centers be clarified through guidance to ensure closer consultation between centers at appropriate times.

ADDENDUM

Outline of Requirements for Implementation

A. The OCP has the authority, by statute, to make these enhancements

- The plain language of the statute establishing OCP; law of combination products
 - Among the responsibilities given to the OCP by statute include "consistent and appropriate postmarket regulation of like products subject to the same statutory requirements."
 - In addition, the OCP is charged with "coordinating reviews involving more than one agency center."
 - The statute also gives the OCP authority to "review each agreement, guidance, or practice . . . specific to the assignment of combination products to agency centers and . . . determine whether the agreement, guidance or practice is consistent with requirements of [the statute]."
- Congress mandated these specific duties for the OCP, with the intent to ensure timeliness of review, and consistency of treatment between like products. To that end, Congress gave the office broad authority. See H.R. Rep. 107-728.
- Within this statutory mandate, OCP has the authority to clarify the combination products process, prepare and review guidances, and to serve as project manager for reviews.

B. Many of these enhancements can be made in the short-term, within the existing statutory scheme.

- Most of the recommended enhancements are consistent with existing statutes.
- In fact, in most cases, new regulations are not required. New guidances or modifications to existing guidances can accomplish the enhancements. For example:
 - Labeling guidances: (1) Clarifies cross-labeling requirements for virtual combination products; (2) adopts the most appropriate reviewing time for labeling changes; and (3) clarifies the format and content requirements for labeling of combination products, particularly if a single integrated label is required.
 - Modification of approved combination products: (1) Clarification of the 510(k) guidance to specifically include modification of certain combination products, including virtual combinations and

kits; and (2) development of a new guidance incorporating a decision tree that guides decision making regarding which modification rules will apply more generally.

- Reporting guidances: Clarification of how the existing rules for drugs, devices and biologics should be applied to reporting of combination product incidences, including a decision tree to guide such decisions.
- Quality systems: Recommended enhancements require only clarification through guidance of which regulatory scheme will apply in certain cases. As envisioned, this will be accomplished within the existing regulatory schemes.
- Clarification of roles.

C. The FDA has the authority, through regulations, to make the remaining enhancements.

- In some cases, rulemaking may be required
 - Labeling: In the long-term, establishing distinct content for combination product labeling would require rulemaking
 - Modifications: Ultimately, modification of combination products approved by CDER may require a separate process that is promulgated by regulation; in the short-term, however, we believe a risk-based decision-making process can help guide how modifications will proceed, consistent with existing statute and regulations. (Ex: Labeling content; single reporting structure)
- Such rulemaking is within the statutory authority given to FDA

D. Some long-term enhancements may require a statutory change

- Reporting: Development of a globally-harmonized, single reporting scheme could require a change to existing statutes.

IV. Conclusion

As scientific advancement gives rise to more and more combination products, FDA and manufacturers will continue to struggle with the issues raised by regulation of combination products, unless those issues are addressed now. For that reason, we urge FDA to work with combination product manufacturers and other stakeholders to develop and implement appropriate solutions to address these issues.

The solutions largely rest in the administrative realm, and can be made without Congressional intervention. Through guidances in most cases, and regulations in others, FDA can eliminate

much of the duplication, conflict and confusion within the current system. Ultimately, this will lead to a more effective and efficient system, assure the availability of important new products, and give greater comfort that the combination products on the market are being used in a way that is safe and effective.