Contains Nonbinding Recommendations

Guidance for Industry and FDA Staff:

Early Development Considerations for Innovative Combination Products

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U.S. Department of Health and Human Services
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Office of the Commissioner
Office of Combination Products

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Public Comment

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I. INTRODUCTION

This document provides guidance to industry and FDA staff on developmental considerations for innovative products that combine devices, drugs and/or biological products. It is intended to provide a context for initial discussions on the type of scientific and technical information that may be necessary for investigational or marketing applications for these combination products.

This guidance focuses on combination products as defined under 21 CFR 3.2(e). The concepts may also be useful for the co-development of devices, drugs, and biological products that are used concomitantly but which do not meet the regulatory definition of a combination product.

This information supplements existing guidance documents developed by the Center for Biologics Evaluation and Research (CBER), the Center for Devices and Radiological Health (CDRH), the Center for Drug Evaluation and Research (CDER), and the Office of Combination Products (OCP).

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

[1] This guidance has been prepared by the Center for Devices and Radiological Health, the Center for Biologics Evaluation and Research, the Center for Drug Evaluation and Research, and the Office of Combination Products in the Office of the Commissioner at the Food and Drug Administration.

II. BACKGROUND

FDA recognizes that innovative technologies may raise a spectrum of scientific and technical development issues. Combination products are increasingly incorporating cutting edge, novel technologies that hold great promise for advancing patient care. Innovative drug, biological product, device combinations have the potential to make treatments safer, more effective, or more convenient or acceptable to patients. For example, drug-eluting cardiovascular stents may reduce the need for repeated surgery by helping to prevent the restenosis that may occur after stent implantation. Drug and biologic products can be used in combination to potentially enhance the safety and/or effectiveness of either product used alone. Proteins incorporated into novel orthopedic implants may facilitate the regeneration of bone required to permanently stabilize the implants. Drug-device inhalation systems provide a new route of insulin delivery that may decrease the need for insulin injections. Genomic-based diagnostic devices may be used to help determine whether certain patients are suitable candidates for a drug or biological product, or at risk for certain types of adverse events.[2]

During an FDA workshop entitled, "*Innovative Systems for Delivery of Drugs and Biologics: Scientific, Clinical and Regulatory Challenges*," industry and academic stakeholders requested that FDA provide guidance for the development of innovative technology that may challenge existing approaches.[3] For example, what pre-clinical or animal studies are appropriate to begin human studies, or what types of clinical trial designs may be appropriate? Further, FDA recognizes that combination product development may raise a number of Critical Path[4] challenges to progress from a novel concept to an innovative marketed product.

Some of these developmental challenges may not be readily apparent. For example, although a combination product may be comprised of an already approved drug and an already approved device, new scientific and technical issues may emerge when the drug and device are combined or used together. New methodologies may need to be developed for manufacturing, evaluation of preclinical safety in targeted areas of the body, or clinical trial design to establish safety and effectiveness.

FDA websites contain a wide variety of guidance documents for the development and testing of drugs, devices, and biological products. These address drugs, devices, or biological products as individual products, but few guidance documents currently address the scientific and technical issues to consider when combining drug, device, and/or biological product constituent parts as a combination product..

FDA believes it is important to address the scientific and technical issues raised by innovative combination products in order to develop efficient, appropriate techniques and methods to ensure the safety, effectiveness, and quality of the combination product.

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[2] Drug-pharmacogenomic test pairings may be considered combination products, depending how the products are intended for use and labeled. FDA is developing separate guidance for the co-development of drug and genomic-based diagnostic devices, and these types of products are not specifically addressed in this document.

[3] A summary of the workshop is available at http://www.fda.gov/oc/combination/workshop070803.html. A transcript is available at http://www.fda.gov/ohrms/dockets/dockets/03n0203/03n0203.htm.

[4] See *The Critical Path to New Medical Products* at http://www.fda.gov/oc/initiatives/criticalpath/.

A. Definition

As defined in 21 CFR 3.2(e), a combination product is a product comprised of any combination of a drug and a device, a biological product and a device, a drug and a biological product, or a drug, device, and a biological product. This includes:

- "A product comprised of two or more regulated components; i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity;

- 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;

- 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; e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or

- 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."

For purposes of this guidance, a constituent part of a combination product is an article in a combination product that can be distinguished by its regulatory identity as a drug, device, or biological product, as defined in section 21 U.S.C. 321, Federal Food, Drug, and Cosmetic Act (Act), and 42 U.S.C. 252 (i), Public Health Service Act, and as set forth in 21 CFR 3.2(k). For example, a device coated or impregnated with a drug has two constituent parts, the device constituent and the drug constituent. For simplicity, the concepts in this guidance are described in the context of a combination product composed of two constituent parts. These concepts are also relevant for combination products with more than two constituent parts.

B. How are combination products regulated?

FDA's Office of Combination Products (OCP) was established in 2002 as required by the Medical Device User Fee and Modernization Act of 2002. As set forth in section 503(g) of the Act, OCP is responsible for the prompt assignment of a lead Agency center that will have primary jurisdiction for the review and regulation of a combination product; ensuring timely and effective premarket review by overseeing the timeliness of and coordinating reviews involving more than one agency center; ensuring consistent and appropriate postmarket regulation of combination products; and resolving disputes regarding the timeliness of combination product

review. OCP also works with agency centers to develop guidance and regulations to make the regulation of combination products as clear, consistent, and predictable as possible. Under section 503(g)(1) of the Act, a combination product is assigned to a center with primary jurisdiction, or a lead center, based on a determination of the primary mode of action (PMOA) of the combination product. PMOA is defined as "the single mode of action of a combination product that provides the most important therapeutic action of the combination product." For example, if the PMOA of a device-biologic combination product were attributable to its biological product constituent, the Agency component responsible for premarket review of that biological product would have primary jurisdiction for the combination product. The final regulation also includes an assignment algorithm that the Agency will use when the most important therapeutic action of a combination product cannot be determined with reasonable certainty.[5]

A combination product is assigned to one of the Agency's three human medical product Centers: CBER, CDER, or CDRH. The lead center has oversight responsibility for the review and regulation of the combination product. The lead center often consults or collaborates with other agency components and OCP, as appropriate, to identify and evaluate the information needed for a regulatory submission (e.g., investigational application or marketing authorization).

In streamlining the review of combination products, FDA established a Standard Operating Procedure for the Intercenter Consultative and Collaborative Review Process.[6] The document provides the policies and procedures for FDA staff to follow when requesting, receiving, handling, processing, and tracking formal consultative and collaborative reviews of combination products, devices, drugs and biologics. The objectives of the SOP are to ensure timely and effective intercenter communication on combination products, as well as the timeliness and consistency of intercenter consultations and collaborations.

This guidance describes general information on developmental considerations for products that combine devices, drugs, and/or biological products. Although details on the regulatory processes described in this section are beyond the scope of this guidance document, FDA encourages developers to contact OCP for assistance in determining the assignment of a lead center when jurisdiction is unclear or in dispute, the number and type of marketing applications[7], the

[5] See final rule for *Definition of the Primary Mode of Action of a Combination Product*, published August 25, 2005, Federal Register, http://www.fda.gov/OHRMS/DOCKETS/98fr/05-16527.pdf

[6] See Intercenter *Consultative/Collaborative Review Process* at http://www.fda.gov/oc/combination/consultative.html.

[7] For most combination products, a single marketing application is sufficient for the product's approval, clearance or licensure. In some cases, however, a sponsor may choose to submit two marketing applications for a combination product when one application would suffice. For example, a sponsor may choose to submit two applications in order to receive some benefit that accrues only from approval under a particular type of application (e.g., new drug product exclusivity, orphan status, or proprietary data protection when two firms are involved). In other cases, FDA may determine that two marketing applications are necessary. For example, when one of the individual constituent parts of a combination product is already approved for another use, and where the labeling of the already approved product will need to be changed to reflect its new intended use in the combination product, FDA may determine that two applications are necessary if the labeling of the already approved product is subject to legal requirements different from those that will apply to the combination product. FDA encourages applicants who are uncertain as to whether a single or multiple marketing applications should be submitted for a combination product to discuss the issue with the lead reviewing Division and/or OCP. Information about the applicable time frames is provided in the

premarket review process, and the postmarket regulations such as adverse event reporting or good manufacturing practice requirements that may be appropriate for a combination product. OCP will work with the agency Centers as appropriate to facilitate a response. Additional information on combination product regulation, guidance, and process is available on OCP's website.[8]

III. GENERAL DEVELOPMENT CONSIDERATIONS

As with other medical products, combination product development typically focuses on the scientific and technical issues raised by the particular product being developed. For a combination product, these scientific/technical issues will ordinarily reflect the combination product itself as well as its constituent parts. When combining products such as drugs or biologics and devices that are customarily developed using different regulatory paradigms, certain critical developmental issues, such as the interaction of the drug/biologic and device constituents, may not be readily apparent. Further, because of the breadth, innovation and complexity of combination products, there is no single developmental paradigm appropriate for all combination products.

Existing guidance documents are generally excellent starting points for considering the types of issues raised by the constituent parts of a combination product, but often they will need adaptation to fully address the combined nature of a combination product. For example, guidance for preclinical evaluation of drugs/biologics differs from the preclinical/non-clinical studies conducted for devices. When developing a combination product, it is likely that neither isolated approach would fully address the relevant preclinical development questions for both constituents as well as for the combination product as a whole. Instead, FDA recommends that developers consider the scientific and technical issues raised by the combination product and its constituents and propose an approach that appropriately addresses these issues without requiring duplicative or redundant studies.

In many circumstances, the development considerations depend on the type of combination product. When the combination product is comprised of constituents that are chemically, physically or otherwise combined or mixed and produced as a single entity, developers should consider and, as appropriate, evaluate the potential for a broad range of drug/biologic/device interactions. For example, for a drug eluting stent, the mechanical attributes of the polymer coating system that contains the drug substance are important for stent deployment, drug release, biocompatibility, and stability. For some combination products, the constituents may have synergistic effects that should be evaluated. In the context of these studies, it is appropriate to discuss approaches to avoid duplication/redundancy and to develop strategies to streamline the overlapping aspects of development.

Innovative new technology may also challenge existing approaches for product development. For example, a new device used to deliver a drug/biologic to a new area of the body that was

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guidance document "Submission and Resolution of Formal Disputes Regarding the Timeliness of Premarket Review of a Combination Product," available at http://www.fda.gov/oc/combination/dispute.pdf.

[8] See OCP's website at http://www.fda.gov/oc/combination.

previously inaccessible might make it necessary to develop new methods to determine the effect of such localized/targeted delivery, particularly when it results in higher exposure to that target than when the drug is systemically administered. Likewise, innovative technologies such as nanotechnology or live cellular products may lead to the development of new manufacturing methodologies or unique safety issues not associated with products manufactured in other ways.

The following sections describe general principles to consider when developing information to demonstrate the safety and effectiveness of a combination product and its constituent parts. We recommend that combination product developers particularly consider the preclinical and non-clinical testing that should be conducted for their product, and how such testing may be influenced by the interaction of the constituent parts, and any prior approval/clearance of a constituent part. FDA believes that the general principles described in this guidance document would assist developers in providing the appropriate data to help establish the safety and effectiveness of innovative combination products. Consideration of these issues in the context of existing guidance documents may lead to a more targeted and efficient development pathway for the combination product.

IV. CURRENTLY MARKETED PRODUCT CONSIDERATIONS

Prior FDA approval and/or clearance of a particular constituent part of a combination product is often an excellent starting point for considering the appropriate data to establish safety and effectiveness for its use in a combination product. FDA recommends that developers fully consider what is already established about a constituent part; i.e., what existing information and data are available, to avoid duplication and ensure a more timely and efficient development process. Throughout the development process, however, it is critical to recognize that it is the *combination product* that is being developed for approval/clearance, not just the constituent part. While this prior information is often very helpful, developers should recognize that additional data and information may be necessary to address the scientific and technical issues raised by the new use of the constituent in the combination product. These issues may be raised by combining the constituent parts or by new uses for the constituent in the combination product, such as a new indication for use, a different target population, a new route of administration, or by different local or systemic exposure profiles once the products are combined. For example, developers should consider:

- Are the constituent parts already approved for an indication?
- Is the indication for a given constituent part similar to that proposed for the combination product?
- Does the combination product broaden the indication or intended target population beyond that of the approved constituent part?
- Does the combination product expose the patient to a new route of administration or a new local or systemic exposure profile for an existing indication?
- Is the drug formulation different than that used in the already approved drug?
- Does the device design need to be modified for the new use?
- Is the device constituent used in an area of the body that is different than its existing approval?

- Are the device and drug constituents chemically, physically, or otherwise combined into a single entity?
- Does the device function as a delivery system, a method to prepare a final dosage form, and/or does it provide active therapeutic benefit?
- Is there any other change in design or formulation that may affect the safety/effectiveness of any existing constituent part or the combination product as a whole?
- Is a marketed device being proposed for use with a drug constituent that is a new molecular entity?
- Is a marketed drug being proposed for use with a complex new device?

As illustrated in the following sections, FDA recommends that the developmental studies should take into account these questions as appropriate for the constituent parts alone and for the finished combination product. FDA furthermore recommends that these issues be considered in the context of the proposed indication.

V. PERSPECTIVES BY CONSTITUENT PART

A. Device constituent considerations

For new device constituent parts, some safety and/or effectiveness testing of the device alone may be necessary before or along with the studies to establish the safety and effectiveness of the combination product as a whole. For device constituent parts that are already approved/cleared for another purpose, the extent of preclinical testing largely would focus on the new use of the device constituent as part of the combination product. For example, if a combination product incorporates an indwelling, intravenous drug delivery catheter for a new use for long-term, drug delivery in the brain, new biocompatibility studies may be necessary to establish the safety of the device materials for placement in neural tissues. New engineering or functional testing may also be necessary to establish the suitability of the device design to the new environment in which it will be used.

Consideration should also be given to the potential interaction (desired or undesired) between the device and the drug/biological constituents. For example, it may be appropriate to conduct studies to evaluate the potential for the following:

- Leachables/extractables of the device materials into the drug/biologic substance or final combination product;
- Changes in stability of the drug constituent when delivered by the device or when used as a coating on the device;
- Drug adhesion/absorption to the device materials that could change the delivered dose;
- Presence of inactive breakdown products or manufacturing residues from device manufacture that may affect safety, or device actions that could change the drug performance characteristics at the time of use; or
- Changes in the stability or activity of a drug constituent when used together with an energy emitting device.

Likewise, similar consideration should be given to the effects a drug or biological product may have on the device constituent. For example, the material properties of a delivery catheter may be adversely affected by some drug/biologic products but not others.

CDRH has an active program of evaluating and recognizing consensus standards.[9] For many combination products, it may be appropriate to use these existing consensus standards for the device constituents of a combination product, including the standard test methods. For others, particularly those that are innovative, it may be appropriate to adapt these standards, or it may be necessary to develop new methodologies. Because of the range of combination products and developmental strategies, developers are encouraged to seek early discussions with FDA when exploring the application of standards to candidate constituent parts and when alternative methodologies or approaches are being developed.

B. Drug and biological product constituent considerations[10]

When a new molecular entity (NME) is a constituent part of a combination product, it is critical to consider what information is necessary to characterize the safety and effectiveness of the NME when used in the combination product. Generally this begins with a consideration of the NME alone; e.g., the preclinical information necessary to begin the initial studies in human subjects of the NME and the information needed for combination of the NME and the device constituent. For example, certain conventional pharmacology and toxicology studies may be necessary to establish the safety profile of the NME alone (e.g., genotoxicity, mutagenicity, immunotoxicity, and local tolerance) before beginning clinical investigation of the combination product.[11] It is also important to consider the timing to initiate any necessary reproductive and carcinogenicity studies; these types of studies are generally conducted after beginning the clinical investigation, and they are generally submitted in the marketing application for the product.

When the combination product contains a drug/biologic constituent that is already approved for another use, we recommend that the developer address the potential for change in the established or understood safety, effectiveness, and/or dosing requirements posed by the new combination. The following are examples of when additional preclinical or clinical safety information or new clinical studies may be appropriate for the drug/biologic constituent and/or the combination product:

1. Approved drug or biological product with a change in formulation, strength, route of administration, or delivery method;
2. New dosage (e.g., absolute dose, dosing duration, dosing regimen, or total exposure);

[9] See consensus standards recognized by FDA http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm.

[10] For purposes of this discussion, the term drug applies to drug and most biological product constituent parts.

[11] See *Guidance to Industry: Format and Content of Non-clinical Pharmacology/Toxicology Section of an Application at* http://www.fda.gov/cder/guidance/index.htm. General pharmacology-toxicology guidances may also be found at this location.

3. New patient population, (e.g., pediatric, geriatric, pregnant or nursing women, or change in disease or disease status); or
4. Change in approved indication.

Regardless of the approval status of the drug/biologic constituent, the marketing application should contain appropriate data to establish the overall safety and effectiveness of the proposed new dosing regimen or indication as proposed in the combination product. For a combination product with a drug or biological product constituent that is already approved, it may be possible to tailor the pre-clinical development program to address safety questions posed by the new route or method of delivery, or the change in indication or population. The goal of these studies would be to evaluate changes that may result in a different extent or distribution of drug constituent exposure.[12] To the extent that the combination product permits local or systemic drug exposure that is greater than that occurring with approved dosing regimens, additional safety studies may also be needed to address the higher doses. New studies may be appropriate to evaluate the local/regional toxicity of a drug/device combination product administered directly to targeted tissue.

Other possible considerations when devising a development plan for a product incorporating a drug/biologic constituent include:

- *In vivo* pharmacokinetic (PK) studies may be necessary to assess changes in formulation, strength, route of administration, dosing, population or other factors that may alter the extent or time course of systemic exposure. These studies might be used to determine drug release kinetics such as release rate, local peak concentrations of the drug, local distribution and systemic bioavailability (C_{max}, T_{max}, etc.).
- Dose ranging or dose finding studies[13] in humans may be appropriate to determine dose adjustments for safety/effectiveness when therapy is targeted to a local site.
- Acute and repeat dose toxicity studies using the new route of administration or method of delivery may be appropriate to determine the NOAEL (no observed adverse effect level) and toxicity profile of the combination product. Typically, these studies would evaluate the intended clinical formulation and dosing regimen/frequency that will closely approximate its use in clinical settings.
- Special safety studies may be appropriate for certain patient populations or risk profiles; e.g., hepatotoxicity, QT prolongation, special populations.
- Specific safety monitoring in the clinical study may be appropriate to obtain data on the novel aspects presented by the combination product; e.g., local toxicity for a new route of administration.[14]

[12] See *Guidance to Industry: Exposure-Response Relationships - Study Design, Data Analysis, and Regulatory Applications* at http://www.fda.gov/cder/guidance/5341fnl.doc.
[13] See *ICH E4 Dose-Response Information to Support Drug Registration* at http://www.fda.gov/cder/guidance/iche4.pdf.
[14] See *ICH E1A: The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions* at http://www.fda.gov/cder/guidance/iche1a.pdf.

In some instances, developers may be able to provide relevant information from the literature or may rely on prior agency findings to address these issues. When this is not possible, then additional studies may be necessary.

VI. ADDITIONAL PERSPECTIVES

A. Clinical Investigation

For most combination products, one investigational application (Investigational New Drug (IND) or Investigational Device Exemption (IDE) application) is submitted for the clinical investigation of the combination product as a whole. Generally, the regulatory guidance for INDs and IDEs provides substantial flexibility in considering how to address the issues posed by a particular product. Two such guidance documents that may be of interest to combination product developers are: (1) *Exploratory IND Studies*, which provides an alternative for exploring candidate products during research and development prior to selecting the composition for further development,[15] and (2) guidance on changes that may occur during investigational development of a device.[16]

Clinical development questions frequently arise about trial design, sample size, statistical methods, clinical endpoints, appropriate number of clinical studies, and appropriate indications/claims. We recommend that you consider the science and technology of the combination product when determining sample size, use of statistical approaches, surrogate endpoints, techniques to measure drug levels in areas not typically accessible, or techniques to evaluate drug-device interactions. Although these issues are beyond the scope of this guidance, FDA encourages developers to seek early discussion with the Agency around these concerns.

For certain combination products that include a device constituent part, it may be necessary to evaluate the human factors of device use on the safety and effectiveness of the combination product. Such studies would evaluate how users operate the system in realistic, stressful conditions. In many cases, these studies include an assessment of all components and accessories necessary to operate and properly maintain the device; e.g., controls, displays, software, logic of operation, labels, instructions, analysis of critical tasks, use error hazard and risk analysis. We recommend that human factors evaluations take place early in the combination product development process to identify design features that may need modification before conducting the key studies to establish the safety and effectiveness of the combination product.

[15] See *Guidance to Industry and Reviewers: Exploratory IND Studies* at http://www.fda.gov/cder/guidance/7086fnl.pdf.

[16] See *Guidance to Industry: Changes or Modifications During the Conduct of a Clinical Investigation* at http://www.fda.gov/cdrh/ode/guidance/1337.pdf

B. Manufacturing considerations

Manufacturing, scale-up, and quality management[17] are important considerations during the development of a combination product. Manufacturing methodologies affect both premarket development and postmarket regulation. FDA encourages consideration of the manufacturing issues posed by the scientific and technical aspects of the drug, biological product, and device constituent parts, and of the combination product as a whole. FDA also encourages developers to carefully consider the effect of the manufacturing methods on the interaction of the constituent parts. For example, the stability of a combination product as a whole may be different than that of the separate constituent parts. Certain drug or biological product constituent parts may be altered or destroyed by terminal sterilization techniques. For constituent parts that use aseptic manufacturing techniques, developers are encouraged to implement manufacturing techniques to ensure aseptic control for the combination product.

During premarket investigation, once the preclinical and clinical studies begin, any potential change in the manufacturing process for the drug, biologic, or device constituents or for the combination product may affect the safety or effectiveness of the combination product as a whole. For example, changes in concentration, inactive ingredients, software, or in the methods to combine two constituent parts, could affect the performance characteristics of the combination product. When applying cellular constituent parts to a device, the performance characteristics may vary with the time and methods used for cellular incubation before application to the device constituent. Additionally, the applicable device constituent design controls would consider anticipated manufacturing changes during investigational development. In order to address such manufacturing considerations, it may be necessary to develop new manufacturing techniques, in-process testing, testing specifications, and other characterization methods to assess changes in the constituent parts and for the combination product as a whole. For certain developmental changes, additional bridging studies (in vitro, preclinical, or clinical) may be appropriate.

In addition to considering manufacturing changes that may occur during premarket development, FDA also recommends early consideration of anticipated postmarket manufacturing changes for the combination product or its constituent parts. FDA encourages manufacturers to establish arrangements with the manufacturers of constituent parts to maintain sufficient awareness of manufacturing changes in constituent parts that may occur during the premarket or postmarket period. Such awareness could help to ensure continued safety and effectiveness of the combination product by ensuring that the potential impact of a manufacturing change is evaluated in a manner appropriate for the stage of combination product development. As appropriate, these postmarket manufacturing changes may require careful review, validation and prior approval before marketing. For some products, it may be helpful to develop post-approval change protocols for further discussion with the Agency.

[17] FDA's current thinking about good manufacturing practices for combination products is described in "Draft Guidance for Industry and FDA Staff: Current Good Manufacturing Practice for Combination Products," available at http://www.fda.gov/oc/combination/OCLove1dft.html. FDA intends to propose current good manufacturing practice regulations for combination products; see the April 24, 2006 Federal Register (71 FR 22565).

C. Reliance on information not developed by the applicant

Investigational or marketing applications often contain trade secret or confidential commercial information. In some instances, developers may wish to provide all necessary information in one marketing application. However, for combination products being developed by more than one manufacturer, there may be a desire to provide necessary information to FDA while maintaining the confidentiality of each manufacturer's intellectual property. This can be accomplished by the application holder submitting to FDA a letter of authorized cross reference from the owner of the referenced material. This letter would grant FDA permission to consider the referenced material in its review of the current application. In general, the referenced information may be available from two sources:

1. Existing application: An existing investigational application (IND or IDE) or an existing marketing application (NDA, BLA, PMA or 510(k)) may provide information relevant to a new developer's application. In some instances, the application being cross referenced may be under co-review for use in the combination product. In other instances, the cross-referenced application may be approved for other purposes, but may have information relevant to the new use.

2. Master file: Master files provide an administrative method to submit confidential information to FDA when an appropriate investigational or marketing application for the constituent is not available. A master file is not a substitute for an investigational or marketing application. FDA neither approves nor disapproves master files; rather, information in a master file is considered in the context of a particular investigational or marketing application. It should be recognized that the information in a master file may be sufficient to support a marketing application for one product, while additional information may be necessary to support its use in another product. For example, this may occur when specific issues raised by the new use of a constituent are not addressed in the master file. Such information could be provided by supplementing the existing master file, or by providing the necessary information in the application under review. More information on drug master files may be found in 21 CFR 314.420 or at http://www.fda.gov/cder/dmf/index.htm. More information on device master files is available at http://www.fda.gov/cdrh/dsma/pmaman/appdxc.html#P7_2.

VII. EARLY INTERACTION AND COMMUNICATION WITH FDA

FDA strongly encourages early communication and discussion between developers, FDA review components and, as appropriate, OCP. Early dialogue allows developers to obtain initial feedback on the kinds of preclinical and clinical testing that may be necessary. Such communication may identify critical issues for product development and help to ensure an efficient development and approval process. Further, early and frequent communication provides the opportunity for FDA to establish its intercenter review team and to develop the

appropriate scientific expertise to facilitate timely and efficient reviews of any future submissions.

CBER, CDER and CDRH provide guidance on milestone/collaboration meetings throughout the development process and submission of investigational and marketing applications. Pre-investigational (pre-IND and pre-IDE) meetings are particularly useful for discussing innovative combination products. Pre-marketing application meetings are also helpful to discuss application content, as well as the sequence and timing of modular applications or when more than one marketing application will be submitted for the combination product. Guidance on how to arrange developmental meetings can be obtained on the CDER,[18] CBER[19] and CDRH[20] websites.

The lead center should be contacted to schedule meetings in accordance with the procedures and milestones applicable to the lead center. We encourage developers to request participation from relevant review components from both the lead and consulting Centers, where appropriate. In addition, OCP is available formally or informally to address jurisdictional, developmental, premarket review, and postmarket concerns.

A. Where may I obtain additional information?

OCP is available as a resource to developers and review staff throughout the lifecycle (assignment, development, premarket review and postmarket regulation) of a combination product. The Office can be reached at (301) 427-1934 or by email at combination@fda.gov. In addition, the Office maintains an updated list of FDA guidance documents that developers may find helpful in the development of their products. The guidance is available at the Office's Internet Website at http://www.fda.gov/oc/combination.

In addition each center maintains a guidance webpage that provides comprehensive information on the types of constituents regulated in the center. The CDER Guidance webpage is accessible at http://www.fda.gov/cder/guidance/index.htm. The CDRH Guidance web page is accessible at http://www.fda.gov/cdrh/guidance.html and the device advice webpage is assessable at http://www.fda.gov/cdrh/devadvice/. The CBER Guidance web page is accessible at http://www.fda.gov/cber/guidelines.htm.

[18] See http://www.fda.gov/cder/guidance/3683fnl.pdf.
[19] See http://www.fda.gov/cber/gdlns/ind052501.htm.
[20] See http://www.fda.gov/cdrh/devadvice/ide/print/approval.html , and, *Early Collaboration Meetings Under the FDA Modernization Act, Final Guidance for Industry and CDRH Staff*; http://www.fda.gov/cdrh/ode/guidance/310.html