September 15, 2011

VIA ELECTRONIC MAIL AND FIRST-CLASS MAIL

Dr. Jonathan Sackner-Bernstein
Center for Devices and Radiological Health
U.S. Food and Drug Administration
10903 New Hampshire Ave.
Building 66, Room 5410
Silver Spring, MD 20993

Re: Docket No. FDA-2011-N-0063; Medical Device Innovation Initiative

Dear Dr. Sackner-Bernstein:

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" or "Agency") can accelerate the development and regulatory evaluation of innovative medical devices, including combination products. The CPC supports FDA’s initiative to enhance the development and regulatory review of innovative medical products, including innovative combination products. Our comments are intended to highlight how combination products should be considered under this initiative.

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 the issues surrounding FDA’s support of innovation.

We are very pleased the Agency has undertaken this initiative. Combination products often incorporate novel devices and other technologies that hold great promise for making treatments safer, more effective, and more convenient or acceptable to patients. At the same time, these innovative combination products raise complex issues during their development and marketing application review. These issues do not disappear once a device is combined with a drug or biological product; indeed, often they increase.

In this regard, below we offer comments on how combination products should be considered under the innovation initiative. One aspect is with respect to clinical research, as there is an acute need for guidance and a stronger infrastructure with respect to research on combination products. Combination products incorporating medical devices also need clarity on
a parallel review pathway to help ensure the Center with the greatest expertise in the issues raised by a combination product’s constituent part has primary responsibility for that part’s review.

Below we provide some examples of innovative combination products, then describe our specific comments and recommendations.

I. INNOVATIVE COMBINATION PRODUCTS

At a general level, the Agency has recognized that “combination products increasingly use state-of-the-art innovative technologies that challenge existing regulatory and scientific knowledge.”

Below we describe some of these products. This is by no means an exhaustive list. Rather, we simply want to provide practical flavor to our comments regarding the inclusion of combination products within the innovation initiative.

Examples of Innovative Combination Products

- The MedGenics Biopump – This product involves a process where a small portion of a patient’s skin tissue is converted into a protein-producing “Biopump.” The Biopump is implanted under the patient’s skin and continuously produces and delivers therapeutic proteins. The Biopump has the potential to deliver several months of protein therapy, eliminating the need for frequent injections and potentially aiding in the treatment of anemia, Hepatitis C, Hemophilia, and certain cancers.

- Photodynamic drugs – These drugs require a light source provided by a device to achieve their therapeutic effect. These are used for the treatment of cancer and other diseases that benefit from targeting a therapy at specific areas of the body to limit adverse effects on healthy tissue.

- Electronic microcontroller based drug patch – This product uses disposable electronics to deliver electronic current that generates an ion transfer between the patch and the patient’s skin. This ion transfer is used to deliver drug to a patient.

- Naturally biodegradable nano-engineered polysaccharides – Microparticles, proteins, or other macromolecules are incorporated into a polysaccharide matrix, which is implanted in into a specific anatomical locale to enable localized delivery of a therapeutic treatment.

- Handheld inhaler in which inhalation causes the creation of an aerosol containing particles of drug that are inhaled deep into the lung – The deep lung being narrower and more vascularized allows for fast and more complete absorption into the bloodstream.

---

1 Food and Drug Administration, Office of Combination Products, FY 2009 Performance Report to Congress for the Office of Combination Products
3 http://www.surmodics.com/technologies-delivery-implants.html
4 http://www.alexza.com/about/the-staccato-system
We encourage FDA to take the steps described below to support the development and review of innovative combination products like these.

II. FACILITATING THE DEVELOPMENT AND REGULATORY EVALUATION OF INNOVATIVE COMBINATION PRODUCTS

The CPC believes that combination products should be part of the innovation initiative and urges the Agency to consider their relevance and formally incorporate them as part of initiative. The challenges associated with the development and review of innovative medical devices does not disappear once the device is combined with a drug or biological product; indeed, often it increases. Therefore, when the Agency takes steps to:

- “Facilitate the development and regulatory evaluation of innovative medical devices;
- Strengthen the U.S. research infrastructure and promote high-quality regulatory science; and
- Prepare for and respond to transformative innovative technologies and scientific breakthroughs

the Agency should consider the role and impact on combination products.

Additionally, the Agency should be cognizant of Congressional statements on innovative technologies and should take these into account when implementing the CDRH Innovation Initiative.

a. COMBINATION PRODUCTS AND THE GOALS OF THE MEDICAL DEVICE INNOVATION INITIATIVE

The CPC recognizes that few products will satisfy the requirements for evaluation under the “Innovation Pathway” due to limited resources and the need to ensure timely review of all medical devices. However, CDRH and FDA can take other actions to assist the development and regulatory evaluation of innovative combination products. In particular, we believe guidance regarding the design of clinical and pre-clinical research required for clearance or approval of combination products and an expedited parallel review process for combination products are of primary importance.

1. GUIDANCE ON PRE-CLINICAL AND CLINICAL RESEARCH ON COMBINATION PRODUCTS

As illustrated by the examples above, combination products increasingly incorporate cutting-edge, novel technologies that hold great promise for advancing patient care and making treatments safer, more effective, and/or more convenient or acceptable to patients. At the same time, these innovative combination products raise complex scientific and technical development issues. For example, new scientific and technical issues may arise even when the combination

---

5 Food and Drug Administration, Center for Devices and Radiological Health, CDRH Innovation Initiative 7 (Feb. 2011)
product is comprised of already approved drug, device and/or biological constituent parts. In order to address these issues, new methodologies need to be developed to evaluate the pre-clinical safety of the combination product with respect to targeted areas in the body and for clinical trial design to establish the innovative combination product’s safety and effectiveness.

Additionally, due to their breadth, innovation, and complexity, no single pre-clinical or clinical research paradigm is appropriate for all combination products. Although FDA has developed many helpful guidance documents pertaining to the testing of drugs, devices and biological products as individual products, few of those address the scientific and technical issues that arise when drug, device, and/or biological constituent parts are combined into a combination product. The issues regarding combination product research are many and varied. Rather than attempt to describe them here, please see the Attachment to this comment letter, which is a draft guidance document the CPC submitted to the Agency pursuant to 21 CFR § 10.115(f)(3) entitled “FAQs on Pre-Clinical and Clinical Research on Combination Products.”

To sum, the CPC believes that the issuance of meaningful guidance on pre-clinical and clinical research on combination products is critical to the development of innovative combination products. Specific guidance from the Centers and OCP will greatly facilitate pre-IND, pre-IDE, and discussions applicants have with OCP when developing the pre-clinical and clinical research design plan for a combination product. In light of these issues, we ask that the Centers work together with the OCP to develop meaningful guidance addressing the design of clinical and pre-clinical research on innovative combination products.

2. STRENGTHENING THE RESEARCH INFRASTRUCTURE

The Agency has pointed out that innovative product “development is facilitated by a solid research infrastructure” which must include a strong foundation in regulatory science. The CPC agrees with this statement and in particular with regard to the importance of having institutions and investigators knowledgeable and skilled not only on good clinical practices, but also on the regulatory and scientific issues that may be unique to the innovative technologies incorporated into combination products. We further believe that the innovative initiative improvements should facilitate these researcher attributes.

In this regard, we recommend that FDA add the following criteria to the Certified Medical Device Test Center qualifications:

- The center must have access to individuals or institutions with combination product development expertise, in addition to device development expertise; and
- The center must have the expertise to anticipate and manage medical issues that may arise during the course of clinical studies involving combination products.

---

6 Innovation Initiative at 13. Regulatory science is “the science of developing new tools, standards and approaches to assess the safety, efficacy, quality and performance of FDA-regulated products.” Id.
3. Expedited, Parallel Review of Combination Products

Another challenge in the development and review of innovative combination products is the absence of a well defined “parallel review” pathway. Although primary jurisdiction over a combination product is assigned to a single Agency center, 21 C.F.R. § 3.4(c) specifically permits the separate or “parallel review” of each constituent part of a combination product by different Agency centers. Implementing a well defined “parallel review” pathway will give FDA maximum flexibility in reviewing innovative combination products by ensuring review by the Agency Center with the greatest expertise in the safety and effectiveness issues raised by a combination product’s constituent parts.

In developing the “parallel review” pathway, we recommend FDA:

- Clearly define whether a manufacturer is required or permitted to submit separate applications for each constituent part of a combination product, if utilizing the “parallel review” pathway;
- Clarify that combination products will be subject to only one user fee, regardless of whether separate applications are filed; and
- Clearly define if, or when, a lead Agency center will be assigned under the “parallel review” pathway and the scope of the lead Agency center’s responsibilities.

b. White House Emerging Technologies Interagency Policy Coordination Committee

The White House Emerging Technologies Interagency Policy Coordination Committee (“ETIPC”) was established with the goals of ensuring that regulations addressing health, safety, or environmental concerns do not unjustifiably inhibit innovation, stigmatize new technologies, or create barriers to trade. On March 11, 2011, the Office of Science and Technology Policy, the Office of Management and Budget, and the United States Trade Representatives jointly issued a memorandum outlining broad principles to advance these goals (the “ETIPC Memorandum”). The ETIPC Memorandum recognized that the innovation of emerging technologies requires more than a focus on research and development, it requires appropriate and balanced regulation and oversight.

As explained above, combination products frequently incorporate innovative emerging technologies or are themselves an emerging technology. Therefore, FDA should ensure that it takes into account the goals and principles outlined in the ETIPC Memorandum when implementing the CDRH Innovation Initiative. Specific examples of how FDA should take into account these principles include:

---

7 Office of Science Technology and Policy, United States Trade Representatives, and Office of Management and Budget Office of Information and Regulatory Affairs, Principles for Regulation and Oversight of Emerging Technologies, Memorandum for the Heads of Executive Departments and Agencies (March 11, 2011).
• Ensure flexibility in the regulation of innovative combination products through the development of a parallel review pathway; and
• Actively engage stakeholders and the public in the development of guidance on clinical and pre-clinical research.

**CONCLUSION**

The CPC is fully supportive of the innovation initiative and believes the specific consideration and inclusion of combination products will greatly enhance the outcomes of the initiative. Guidance on the development of pre-clinical and clinical research on combination products and the availability of Medical Device Test Centers with experience in the development of combination products are important steps the Agency can take to foster the initiation of pre-clinical and clinical research and to ensure the research is appropriately designed, thus enhancing patient protections and data integrity. Further, not only will the implementation of a “parallel review” pathway reduce the length of time in enabling patient access to innovative combination products, it also will improve the Agency’s review of each constituent part’s safety and effectiveness by tasking the Agency center with the most expertise and experience with the review of each the separate part.

Respectfully submitted,

Bradley Merrill Thompson, on behalf of the Combination Products Coalition
E-mail: bthompson@ebglaw.com
Direct: 202.861.1817

cc:
Jill Warner, J.D., Acting Associate Commissioner for Special Medical Programs
Thinh Nguyen, Director, Office of Combination Products
Patricia Love, M.D., MBA, Deputy Director, Office of Combination Products
John (Barr) Weiner, J.D., Associate Director for Policy and Product Classification Officer, Office of Combination Products

**Attachment**
Combination Product Coalition, Draft Guidance Submitted to OCP, “FAQs on Pre-Clinical and Clinical Research on Combination Products” (February 2009).
ATTACHMENT

Combination Products Coalition, Draft Guidance Submitted to OCP, “FAQs on Pre-Clinical and Clinical Research on Combination Products” (February 2009).
February 27, 2009

VIA FEDERAL EXPRESS

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

Re: Guidance Document Submission

Dear Sir or Madam:

Pursuant to 21 C.F.R. § 10.115(f)(3), the Combination Products Coalition (“CPC”) is submitting a proposed guidance document entitled Draft Industry and FDA Staff: FAQs on Pre-Clinical and Clinical Research on Combination Products. This draft guidance document is intended to answer questions the combination products industry has posed about issues affecting combination products\(^1\) during pre-clinical and clinical research. Combination products represent some of the most cutting-edge products in development today, and thus present some of the most complex issues during their pre-clinical and clinical research phases. To capture these issues, our organization not only drew on the experience and expertise of its members, but also engaged in dialogue with several other constituents in the combination products industry.

By way of background, the CPC is a group of leading drug, biological product, and medical device manufacturers with substantial experience and interest in the combination products area. One of the principal goals of our organization is to work 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.

Combination products hold great promise for advancing patient care, in part because they increasingly incorporate some of the most highly advanced technologies being developed today. Thus, while combination products have the potential to make

---

\(^{1}\) 21 CFR § 3.2(e).
treatments safer, more effective, or more acceptable to patients, they often raise complex scientific and technical development issues. Importantly, they also involve the intersection of the different regulatory paradigms that apply to drugs, devices, and biological products.

However, currently very few guidance documents specifically address the development and testing of combination products. While certain drug-, biologic-, or device-focused guidance documents may be relevant to combination products, our discussions with industry revealed an acute need for guidance focused specifically on combination product research issues.

For the reasons above, the CPC believes the Agency should develop guidance on issues arising during pre-clinical and clinical research of combination products. We therefore respectfully request the Agency consider the attached draft guidance. If the CPC can help in any way, please do not hesitate to contact us.

Respectfully submitted,

[Signature]

Bradley Merrill Thompson,
On behalf of the Combination Products Coalition

Cc: Thinh Nguyen,
Director of the Office of Combination Products

John (Barr) Weiner
Acting General Attorney, Office of Combination Products
Combination Products Coalition:
Guidance Document Submission

DRAFT Guidance for Industry and FDA Staff:

FAQs on Pre-Clinical and Clinical Research on Combination Products

February 27, 2009

I. Purpose

This document is intended to provide guidance to industry and FDA staff on pre-clinical and clinical research on combination products, defined under 21 CFR § 3.2(e). The agency identified a need for this guidance because of the ways in which combination products increasingly incorporate cutting-edge, novel technologies that hold great promise for advancing patient care. While these innovative combinations have the potential to make treatments safer, more effective, or more convenient or acceptable to patients, they may also raise complex scientific and technical development issues. For example, even when a combination product is 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. Moreover, the combination of drugs or biologics and devices entails the interaction and resolution of the different regulatory paradigms under which the products are typically developed. Finally, because of the breadth, innovation and complexity of combination products, there is no single developmental paradigm appropriate for all combination products.

FDA has developed a number of guidance documents pertaining to the development and testing of drugs, devices, and biological products as individual products. However, few guidance documents address the scientific and technical issues to consider when combining drug, device, and/or biological product constituent parts as a combination product. For these reasons, FDA's Office of Combination Products (OCP) believes that additional guidance on combination product research and development is needed.

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.

II. Background Information
Before addressing the frequently asked questions on the clinical development of combination products, we want to set forth some fundamental background on how combination products are regulated by the agency.

a. What is a combination product?

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. This guidance refers to these types of combination products as “single entity” combination products.

- 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. This guidance refers to these types of combination products as “kit” combination products.

- This guidance also refers to “cross-labeled” combination products, which are defined as follows:
  
  - 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.
  
  - 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.

b. Generally speaking, how are combination products regulated?

The OCP was established in 2002 as required by the Medical Device User Fee and Modernization Act of 2002. 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." Based on its PMOA, a combination product is assigned to one of the Agency's three human medical product Centers: the Center for Biologics Evaluation and Research (CBER), the Center for Devices and Radiological Health (CDRH), or the Center for Drug Evaluation and Research (CDER). 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).

c. What existing FDA guidance documents apply to combination products?

FDA websites contain a wide variety of guidance documents for the development and testing of drugs, devices, and biological products. In particular, OCP has posted a listing of guidance documents that we believe are relevant to combination products, and included among these are general and product-specific guidance documents that may assist with clinical study-related issues: [http://www.fda.gov/oc/combination/guidance.html](http://www.fda.gov/oc/combination/guidance.html).

However, currently few guidance documents address the specific issues encountered during the pre-clinical and clinical development of a combination product. This guidance document is intended to address questions pertaining to those issues, and, therefore, supplements existing guidance documents developed by CBER, CDER, or CDRH, and OCP.

III. Pre-Clinical Safety Studies

a. How can combination product sponsors ensure that preclinical studies are appropriately designed?

The design of preclinical studies varies by the type of product studied and the data that will ultimately need to be included in an IND or IDE. Because of these individualized and unique factors, FDA recommends that sponsors contact their lead Center review division to discuss this issue. Sponsors can also obtain insight into study design by reviewing approval documentation for approved combination products. Finally, FDA also encourages sponsors to consult the guidance documents that are applicable to combination products (See [http://www.fda.gov/oc/combination/guidance.html](http://www.fda.gov/oc/combination/guidance.html)). Examples of guidance documents that might be helpful in the design of preclinical studies include *Exploratory IND Studies, Format and Content of the Nonclinical Pharmacology/Toxicology Section of an Application*, and *Nonclinical Safety Evaluation of Drug or Biologic Combinations*. 
b. How does conducting clinical studies under an IDE versus an IND affect preclinical studies?

FDA believes that this factor alone should not have a substantial impact on preclinical studies. Whether an Investigational New Drug (IND) or Investigational Device Exemption (IDE) application is used, the application may contain information on the entire combination product, as appropriate. With respect to preclinical studies, the focus should remain on safety-related issues applicable to a constituent part that would typically be included.

IV. IND and IDE Applications

OCP receives numerous questions about how the IND and IDE requirements apply to a sponsor. The questions in this section are designed to apply to those process-oriented issues.

a. What determines whether a sponsor should file an IND and/or an IDE?

For most combination products, applicants should submit only one investigational application (IND or IDE) for the clinical investigation(s) of the combination product as a whole. The FDA center with primary jurisdiction over the combination product will determine whether a sponsor should file an IND or IDE. Typically CDRH will require an IDE, and typically CDER or CBER will require an IND.

b. Generally speaking, what content should an applicant include in an IND or IDE for a combination product?

Whether an IND or IDE application is used, the application may contain information on the entire combination product, as appropriate. For example, if the product is a drug-device combination product, the IND or IDE may need to include the details on the drug and device that typically would be submitted in an IND for the drug or biological constituent part and in an IDE for the device constituent part. Of course, the specific content of an IND or IDE will vary based upon the product and its constituent parts. If a sponsor wants to deviate from the typical content of the IND and IDE, FDA recommends discussing the desired approach with the applicant’s lead center.

Additionally, as stated above, there are a number of existing guidance documents that can assist sponsors with issues surrounding the development of combination products. Moreover, generally, the regulatory guidance for INDs and IDEs provides substantial flexibility in considering how to address the issues posed by a particular product. For example, two 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, (See Guidance to Industry and Reviewers: Exploratory IND Studies at http://www.fda.gov/cder/guidance/7086fnl.pdf) and (2) guidance on changes that may occur during investigational development of a device (See Guidance to Industry: Changes or Modifications During the Conduct of a Clinical Investigation at http://www.fda.gov/cdrh/ode/guidance/1337.pdf).
However, because sponsors have approached the agency with a number of questions specific
to combination products, this guidance document is intended to supplement the existing
guidance to address issues that pertain specifically to combination products.

c. How should an applicant incorporate device-related information into a
“regular” IND for drug-device or biological-device combination product,
and how should an applicant incorporate drug-related information into an
IDE for a drug-device or biological-device combination product?

To the extent that an IND needs to include information about a device constituent part, the
agency believes that the IND format and sections are sufficiently flexible to capture device-
related information. For example, many applicants have successfully used the CMC section
of an IND to capture device-related information.

Similarly, to the extent that an IDE needs to include information about a drug or biological
constituent part, the IDE format and sections are sufficiently flexible to capture drug- or
biological-related information.

d. How should an applicant incorporate device-related information into an
IND in the Common Technical Document (“CTD”) format for drug-
device or biological-device combination product?

FDA recognizes that INDs in the CTD format may be less flexible in their application to
combination products than traditionally formatted INDs. However, the agency believes that
an applicant should be able to adapt the CTD format to encompass device-related information.
In particular, many applicants have successfully created new sections in the CTD IND as
required to capture device-related information. One example of this approach would be an
applicant’s use of the regular, drug-related CMC section and creation of a separate, device-
related CMC.

e. To what extent may an applicant suggest or request coordination among
Centers, branches, or divisions in establishing submissions requirements
for a clinical study on a combination product?

The Agency has established policies regarding coordination among Centers, branches, and
divisions with regard to combination products. Additionally, the Agency encourages
applicants to make requests and offer suggestions for how such coordination should occur.
Some ways in which applicants may make these requests and suggestions are by working with
the relevant Project Manager or Branch Chief, or through meeting requests. Please also see
question X.c. in this guidance for more information about meeting requests.

V. Clinical Study Design

a. How does an applicant assess what clinical data are needed for a
combination product?

FDA considers the entire combination product in assessing the data required to support the
product submission. For example, while one part of the product might already be approved,
another part might be new and raise questions about safety or efficacy. The combination of constituent parts may also raise important safety and efficacy issues. Therefore, in planning for clinical studies to support a marketing submission for a combination product, sponsors should consider what parts of their combination product are investigational and require clinical data to support marketing approval, as well as how the parts interact and what data are needed to support claims relevant to that interaction.

For example, in a drug-device delivery system, the data should support claims that the constituent parts are safe and effective for their individual intended purposes, as well as that the product as a whole is safe and effective for its intended use. Clinical data may be required to support all of these uses, although the specific data needed for the product at issue may vary depending upon the approval status of the constituent parts and the type of device part.

Additionally, whether the constituent parts should be evaluated separately, as a system, or both, is a highly variable issue that varies depending on the product, the approval status of the constituent parts, and the applicant’s desired claims (e.g., does each individual product have effectiveness claims). To expand on the drug-delivery delivery system example, consider a needle-free autoinjector. While the applicant should consider the autoinjector’s efficacy separately, the applicant should also evaluate the interaction between the autoinjector and drugs, considering issues such as the rheological effect of shearing forces on macromolecules. However, an efficacy study may not be required if initial testing shows that the drug is not impacted by interaction with the device. As with other individual product issues, the Agency encourages early and frequent discussions between the applicant and the Agency to determine the appropriate development pathway for the product.

b. What inputs should a sponsor use for planning its clinical studies?

In terms of specific inputs for the assessments described above, the impact of the constituent parts together may be evaluated by in vitro testing, CMC/bench testing, or other assessments that are appropriate for the specific product. Another major input is risk assessments, such as end user or usability assessments. These assessments can inform important considerations, such as:

- User training/design validation and the training aspect on how to use the product.
- Anticipated complaints and adverse events.
- Questions and issues to aide in complaint and adverse event investigation. For example, such questions should seek to differentiate which constituent part caused a complaint/adverse event.
- Product packaging and labeling that allows subjects and clinicians to distinguish among the various parts of the investigational product.
- For a drug constituent part, potential over- or under-dosing issues.
- Product return issues and how the product can be appropriately controlled to the extent it represents a biological hazard (e.g., sterilization, EH&S handling specification).
c. What sample size requirements apply to sponsors of clinical studies on combination products?

Beyond the general inputs above, sponsors have asked how they can best assess and determine appropriate sample size for combination product studies. Because combination products involve such a wide range of technology and corresponding risk levels, there may be a multitude of factors impacting issues such as sample size. Specifically:

- The product’s investigational parts and the science and technology of the combination product.
- As with other clinical studies, the type, phase, and objectives of a study are significant factors.
- Existing clinical data.
- Complaint projection rates as determined by internal or external benchmarking. For example, these considerations may drive the development of the sample size necessary to assess and establish adverse event occurrence ratings.
- Primary mode of action of the combination product and which Agency Center is the lead Center for the combination product.

Clearly, these issues are individual to the combination products, and as such, FDA encourages early discussion with the Agency around these concerns. Additionally, existing guidance, including International Conference on Harmonization (ICH) guidelines, can offer assistance to sponsors.

d. How do study design requirements change based upon the type of combination product being studied (e.g., single entity, kit, cross-labeled)?

As mentioned above, FDA considers the entire combination product in assessing the data required to support the product submission, so the type of clinical data needed (and hence study design) will be affected by the parts of the product that require clinical data to support marketing approval. For some new combination products, the clinical data may need to support the entire combination product, particularly when the product’s efficacy claims relate to both constituent parts or when the product is highly integrated. On the other hand, as discussed above, clinical studies may be more limited in scope in situations where a constituent part is already approved, there will be no efficacy claims relating to a product, or the constituent part would not otherwise require data (e.g., a low risk device).

That said, because combination products represent such a wide variety of risk levels, it is difficult to generalize the permutations of study design requirements.

e. How can a sponsor best demonstrate safety across a range of drugs for a drug delivery platform that can be used with a variety of drugs?
One central question here is whether and to what extent sponsors may bridge studies for one drug to the other. If the drug and study population are sufficiently similar, such bridging studies may be possible. Typically, bridging studies will be more suitable when the drug products contain the same drug substance (i.e., are “generational” changes), rather than for a completely new drug product. For example, in terms of drug similarities, sponsors should consider issues such as viscosity, acidity, and light sensitivities. Sponsor should also consider similarities in the study already conducted and the study that would otherwise be needed if a bridging study were not conducted. Factors to conduct include endpoints, patient population and size, inclusion/exclusion criteria, and clinical setting.

Additionally, for drug delivery devices that will be used with a variety of drugs, the applicant may need to conduct testing on multiple drugs and/or representative drugs in a class, in order to support the device’s intended use.

**f. If a combination product uses a device as a delivery system and intends the product for home use, what clinical data should be collected (if any) to support a “home use” claim?**

Medical devices, like other FDA-regulated products, must be safe and effective for the uses for which they are intended. If a device is intended for home use, the sponsor must be able to demonstrate that the intended users are able to operate the device safely and effectively under realistic conditions. For combination products that include a device constituent part, this assessment will likely include an evaluation of the impact of human factors on the safety and effectiveness of the combination product. Such an assessment would evaluate how users operate the system in the home use setting and would cover 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.

FDA has also issued guidance on home use claims specific to diagnostic devices that may be useful input for other products. Here, at a high level, sponsors should demonstrate that:

- the user will get acceptable results from the test compared to the results obtained when a professional performs the test;
- the user will be able to interpret test results correctly; and
- the benefits of the test outweigh its risks.

However, such data development may not necessarily occur in a clinical study setting (see below, Question IV.e.v. Further guidance on home use claims for diagnostic devices can be found at: [http://www.fda.gov/cdrh/oivd/doc-fdareview.html](http://www.fda.gov/cdrh/oivd/doc-fdareview.html)

**VI. Specific Regulatory Requirements**

In addition to questions about investigational product submissions and clinical study design, sponsors often pose questions concerning how specific regulatory requirements that typically apply in the drug, biologic, or device setting should be applied to the development of a combination product.
a. Labeling

i. In a study that is not completely blinded, how should constituent parts be labeled?

Generally, applicants should use the rules that apply to their investigational application – i.e., the IND or IDE rules. As discussed above, clinical studies for most combination products will be conducted under either an IDE or IND (not both). In cases where compliance with these rules presents a conflict or problem for a sponsor, we suggest discussing the issue with your lead Center.

b. Manufacturing Issues and GMPs

i. Are sponsors permitted to manufacturer investigational combination products manually?

Yes, sponsors may manually manufacture investigational combination products as long as the product complies with all controls that ordinarily apply, such as applicable Good Manufacturing Practices (see following questions). Manual manufacturing could be employed throughout the research process. We anticipate that manual manufacturing would most commonly be used for combination products incorporating device constituent parts.

ii. For drug-device combinations under an IND, what drug GMP requirements apply to the device constituent part, given that devices under an IDE are typically exempt from GMP requirements, except for design controls?

For drug-device investigational products under an IND, the relevant drug GMP requirements will depend on the type of combination product. Specifically, for combination products that are produced as a single-entity or are co-packaged, our September 2004 draft guidance on GMPs applicable to combination products recommended that the relevant drug GMPs would apply to the device constituent part during and after joining the constituent parts together. In contrast, under the draft guidance, the drug GMPs would not apply to the device constituent of a cross-labeled combination product, because the device constituent part will only be provided and manufactured separately from the drug or biological constituent parts. For more information, please consult the September 2004 draft guidance on GMPs applicable to combination products: [http://www.fda.gov/oc/combination/OCLove1dft.html](http://www.fda.gov/oc/combination/OCLove1dft.html).

iii. For drug-device combinations under an IDE, what device GMP requirements apply to the drug constituent part? For example, do design validation and/or verification requirements apply to the drug constituent part?

Devices approved under an IDE are exempt from the Quality System regulation (QSR), except for the design control requirements under 21 CFR § 820.30 and those requirements with which the sponsor states its intention to comply in the IDE. As recommended in our September 2004 draft guidance on GMPs applicable to combination products, design controls are one element of the QSR that does not overlap with drug GMPs and should, therefore, be
applied to a drug-device combination products when and to the extent that the constituent parts are physically combined or merged. Therefore, following the recommendations in the draft guidance, for combination products that are produced as a single-entity or are co-packaged, design controls would apply to the drug constituent part during and after joining the constituent parts together. However, the QSR, including design controls, would not apply to the drug constituent of a cross-labeled combination product, because the drug constituent part will be provided and manufactured separately from the device constituent parts. Note that if the sponsor elects to comply with other parts of the QSR these may also apply to a single entity or kit combination product, to the extent those QSR requirements do not overlap with the drug GMPs (e.g., CAPA and purchasing controls – See September 2004 Draft GMP Guidance).

iv. How do risk assessments performed on devices apply to the drug constituent part of a drug-device combination product?

Risk management is essential to and required for the development and control of medical devices and its importance has also been recognized in the pharmaceutical industry. For example, the ICH Q9 guidance outlines the application of risk management for pharmaceuticals and is very similar to ISO 14971, a recognized standard for risk management to medical devices. In all, the Agency and stakeholders alike are increasingly recognizing that quality risk management is a valuable component of any effective quality system. Therefore, we anticipate that most effective quality systems for combination products will incorporate principles of risk management, whether as a direct requirement under applicable device regulations or as an industry best practice.

In this regard, when performing a risk assessment, the manufacturer should consider the probability and severity of the harm or physical injury or damage to health (including the damage that can occur from loss of product quality or availability), or damage to property or the environment\(^1\), that can be caused by a failure of the product. As applied to a combination product, this harm should be assessed with respect to the product as a whole and its constituent parts, regardless of whether the constituent parts are provided as a single entity or otherwise. This stage of the assessment could be completed through performance of a Preliminary Hazard Analysis or a similar assessment. Additional risk assessment techniques should focus on the risk contribution of specific parts of the product or process. The potential problems and/or failures of the drug constituent part, including the process of formulating, storing and combining with the device (if applicable), can be assessed separately in a component or process Failure Modes and Effects Analysis (FMEA) to establish and determine the appropriate mitigation to reduce or eliminate these risks.

One example of the risk assessment process as applied to combination products is with respect to clinical studies. Here, preliminary risk assessments should be completed before the start of the study (based on in-vitro and pre-clinical work) and should be revised based on results provided during the study. Such risk assessments would be applicable to the drug constituent part of a drug-device combination product.

\(^1\) See ISO 14971:2007 and ICH Q9.
v. Should product design validation/user testing requirements be incorporated into clinical studies on combination products?

Combination products that incorporate device constituent parts may need to consider a variety of usability and human factors inputs. For example, the use of the investigational product might be far more controlled (e.g., clinic or in-patient setting) with significant amounts of patient follow-up, than in the final user setting. Therefore, sponsors should consider how users operate the system under stressful conditions. This analysis should encompass all components and accessories necessary to operate and properly maintain the device; e.g., controls, displays, software, ergonomics, logic of operation, labels, instructions, analysis of critical tasks, use error hazard and risk analysis. Importantly, however, clinical studies are often not required to evaluate these portions of design validation. Indeed, the instructions for use (IFU) and training implemented under a clinical study are necessarily different than those that will be implemented for a final marketed product. One purpose of a clinical study is often as a source of Design Input, in that they help to identify changes, additions or revisions to user training and instructions for a final product.

For products where the PMOA is drug or biologic, the role the device constituent part plays in the safety and/or effectiveness of the drug is a critical factor in determining the need for and implementation of device validation and user studies. If the safety and effectiveness of the drug can be established independently from the device constituent part, sponsors may conduct non-clinical, simulated use studies with both quantitative and qualitative measures to validate the usability of the products, including the IFU. These non-clinical methods can be used for the device validation separate from a clinical study, for example, in a small post-Phase III bridging study. The results of these types of studies should be used to evaluate the impact on the drug and can result in product design changes, changes in the IFU, and the identification of the need for and the design of a training program. Unless the product changes arising as a result of these studies impact the drug’s effectiveness, clinical studies should typically not be required. These studies should be discussed and summarized as part of the final submission approval and should be maintained in the master file, thus available for FDA inspection.

For products in which the safety or effectiveness of the drug or biologic cannot be separated from the performance of the device, the inherent nature of the product may necessitate a clinical approach. For example, in highly integrated and high risk products, such as implantable drug-eluting stents, design validation has been a part of clinical study design. However, the use of clinical trials for design validation should not preclude use of pre-clinical and simulated user studies to develop and refine the device use, including instructions and any required training.

Finally, for products in which the drug or biologic plays an ancillary role, if clinical studies are required, these studies may be the culmination of the device validation and should include elements that satisfy the requirements to establish the “usability” of the device and the required instructions, in addition to establishing its safety and effectiveness for the intended use. Earlier (pre-clinical) user groups and/or simulated use user studies may be also be required to fully develop the product that is used in the clinical trial.

VII. Safety Reporting
a. How does a sponsor determine what adverse event reporting requirements apply in a clinical study on a combination product?

Sponsors should use the rules that apply to their investigational application – i.e., the IND or IDE rules. As discussed above, clinical studies for most combination products will be conducted under either an IDE or IND (not both).

b. What adverse event reporting requirements apply when a study involves a combination product comprised of an unapproved or uncleared constituent part and a cleared or approved constituent part?

Adverse event reporting for the investigational constituent part will be governed by the rules of the applicable investigational application – i.e., the IND or IDE rules. If the sponsor markets the cleared or approved product, then the sponsor would report adverse events under the rules that apply to that product (e.g., drug safety reporting requirements, medical device reporting, etc). If a firm other than the sponsor markets the cleared or approved product, we recommend that the sponsor report adverse events pertaining to the marketed product to the firm that markets the product, although the regulations may not require such reporting.

For example, consider a situation in which a sponsor imports a device into the U.S. and has the device shipped to a distributor. The distributor then distributes the device to various clinical sites participating in the research. Here the sponsor may have an obligation to report an adverse event about the marketed device to the original manufacturer because the sponsor is likely to be considered the “importer” of the approved product under the medical device reporting regulations. On the other hand, if the sponsor did not import the device into the U.S. and simply purchased it from a U.S. manufacturer or distributor, the sponsor would ordinarily not have a regulatory obligation to report an adverse event to the manufacturer.

In any event, duplicate reporting of an adverse event to the agency (e.g., from the sponsor and the manufacturer) is not required.

VIII. IRB/Ethics Committee Review

a. How does FDA ensure that IRBs and ECs have adequate combination product expertise?

FDA regulations require that IRB members have “varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution”, and the experience and expertise of IRB members must qualify the IRB to “to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects.” (See 21 CFR § 56.107). Thus, pursuant to agency regulation, it is the IRB’s responsibility to ensure that its members are qualified to review the research that is the subject of IRB’s jurisdiction, and the IRB’s compliance with these requirements would be within the scope of FDA’s inspection of an IRB.

2 21 CFR §§ 803.3; 803.40.
With respect to combination products, sponsors have been confronted with situations in which IRBs are unclear on the regulatory issues surrounding combination products. For example, some IRBs may try to impose drug requirements or standards in a clinical study of a drug-device combination product, even when the PMOA of the product is that of a device and the study is conducted under an IDE. Thus, FDA believes a need exists for IRBs to become more familiar with issues impacting clinical studies of combination products, and this guidance represents one step in that direction.

The agency also believes that sponsors can help ensure IRBs have adequate expertise and experience by researching relevant member experience and, if necessary, by providing materials to help educate IRB members on the investigational product and combination products generally. Taking the example above, such materials could describe the PMOA of the combination product, the significance of the PMOA determination, and how it affects the clinical study process. Such education and informative materials may help in expediting the IRB review process for the combination product.

IX. **Specific Technologies – Prefilled Injection Devices**

In addition to questions on specific regulatory requirements, we also frequently receive questions about the development of a specific type of combination product. In particular, applicants have posed many questions regarding combination products incorporating prefilled injection devices. Therefore, in addition to the general guidance above regarding clinical studies on combination products, below we address some common questions we have received on products incorporating prefilled injection devices.

**What bioequivalence or other bridging studies are required in order to make the following product changes?**

a. a *vial* to a prefilled injection device in a drug-device combination product?

Here the product is being changed from either a drug or biological to a combination product. Therefore, this change involves a significant change to the primary and secondary container closure and should require complete characterization of compatibility and stability, including performance and functional device testing (design verification studies) and design validation studies (user testing). In terms of specific requirements, if there is automated injection with an external power source, the effect on the drug must be assessed. An example of a potential effect on the drug is the rheological effect of shearing forces on macromolecules. Further, if there is a significant change in the method that the needle penetrates the injection site (e.g., needle free injection), a small crossover study establishing the necessary equivalence of the syringe versus the injection device product may be warranted.

b. a *syringe* to a prefilled injection device in a drug-device combination product?

In contrast to the situation above, here the product is already starting from one type of combination product (as opposed to a stand-alone drug or biological product) and is changing to another combination product. Therefore, this change may be more limited than the above example. For example, it may not involve a change to the primary container closure, only to
the functional secondary packaging. (Note, however, that this is not true if the syringe itself is changed and/or the pre-filled injection device has a unique container.) For this more limited change, appropriate supporting data should include performance and functional device testing (design verification studies) and design validation studies (user testing). Generally speaking, no new leachables and extractables, biocompatibility or stability studies would be warranted unless the specific change raises issues in these areas. Additionally, if the additional packaging provides additional light stability, then a photostability study should be done. As with the above example, studies on the rheological effect of shearing forces on macromolecules may also be warranted in order to fully assess the effect on the drug.

X. Agency Process and Communications

Finally, we want to address how a sponsor can obtain agency input on questions regarding combination product development and how to resolve those instances where a conflict arises between a sponsor and the agency.

a. What can a sponsor do if they believe that FDA is being too demanding with respect to what preclinical or clinical studies are required for a combination product?

Sponsors have several different avenues for approaching disputes with the agency. In particular, sponsors are always welcome to contact either the Agency-wide or Center Ombudsmen for assistance in resolving issues and disputes involving the regulatory process and/or the application of Agency policies and procedures. FDA regulations also set forth a process for internal agency review of decisions, such as how sponsors may request review of a scientific controversy by an appropriate scientific advisory panel or an advisory committee (21 CFR § 10.75). The agency has published guidance documents on these procedures as well (See, for example, Guidance for Industry; Formal Dispute Resolution: Appeals Above the Division Level, available at http://www.fda.gov/cber/gdlns/dispute.htm; and Medical Device Appeals and Complaints: Guidance on Dispute Resolution, available at http://www.fda.gov/cdrh/modact/dispresl.pdf; and Resolving Scientific Disputes Concerning The Regulation Of Medical Devices, A Guide To Use Of The Medical Devices Dispute Resolution Panel; Final Guidance for Industry and FDA, available at http://www.fda.gov/cdrh/resolvingdisputes/1121.html).

In addition, OCP is available as a resource to sponsors anytime throughout the product development process for issues pertaining to the development and regulation of combination products. For example, OCP is often a useful resource in assisting sponsors with issues involving inconsistency between or among agency divisions that a sponsor believes is unjustified. In particular, we have found that OCP may act as a “mediator” to help resolve the issues a sponsor has within the Centers.

b. Do sponsors of clinical studies on combination products have the ability to meet with FDA on clinical research issues in addition to existing avenues for pre-IND or pre-IDE meetings?
The agency recognizes that, currently, sponsors have limited access to FDA for input on combination product clinical studies, other than formal pre-IDE and pre-IND meetings. Moreover, FDA recognizes that the special circumstances surrounding clinical trials on combination products demonstrate a need for alternative and additional informal and formal mechanisms for early and continued agency-sponsor communication regarding these products. In particular, many of these sponsor companies are small, start-up companies with limited resources and, for the most cutting-edge combination products, even larger companies are unlikely to have expertise in both device and drug or biologic requirements and will therefore need more “basic” assistance and guidance. Further, to date, very little guidance and precedent exists for many of these products. For these reasons, agency requirements and expectations are likely to evolve on a case-by-case basis and in a manner that is best facilitated by strategic and interactive meetings, rather than the question and answer format of current meetings. Finally, FDA also benefits from education and discussion on the technologies and unique elements of these products, and again, the current meeting format is not always optimal for the type of educational and informative meetings that can provide a foundation for the agency.

In light of the above, sponsors are invited to submit written requests for meetings to discuss product development and clinical research issues to OCP. This request should describe the combination product at issue, describe the issues and relevant questions, and suggest agency personnel who should attend the meeting. OCP will then coordinate with the responsible Centers and individuals. If appropriate, these meetings, which may occur both before and during the clinical development process, may be treated as Type C meetings under existing agency rules.

Additionally, sponsors also have existing regulatory avenues under which they may request agency input. For example, under 21 C.F.R. § 10.85, sponsors may submit a request for an advisory opinion to the Division of Dockets Management. In general, the regulations require the agency to respond within 180 days of receipt of such a request. One benefit of requesting an advisory opinion is that the agency’s response represents the formal position of the agency on the issues involved, thus, except in unusual situations where an immediate and significant danger to health is involved, the agency is obligated to follow its response unless it is amended or revoked pursuant to the relevant regulatory requirements. The agency will not recommend legal action against a person or product with respect to an action taken in conformity with an advisory opinion that has not been amended or revoked pursuant to applicable regulatory requirements. Please see 21 CFR § 10.85 and related sections for additional information about requesting an advisory opinion.