Regulation of Combination Products:

FDA Employee Perspectives

Combination Products Program
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I. Introduction and Methodology

Combination products (defined in further detail in 21 CFR Part 3) are composed of two or more different regulatory entities, i.e., drug-device, drug-biologic, device-biologic, or drug-device-biologic products. Such products often involve cutting edge, novel technologies that raise unique scientific, technical, policy and regulatory issues. Furthermore, the multi-Center aspect of the premarket review and regulation of combination products presents unique challenges in review management. The combination of two distinct components that would normally be regulated under different regulatory authorities introduces additional factors to consider in the assignment of lead Center and the formulation of appropriate regulatory requirements. Stakeholders report that FDA can expect to receive significantly more combination products for review as technological advances continue to merge therapeutic products and blur the historical lines of separation between FDA's medical product Centers.

A number of criticisms have been raised regarding FDA's regulation of combination products. These include concerns about the consistency, predictability, and transparency of the assignment process; issues related to the management of the review process when two (or more) FDA Centers have review responsibilities for a combination product; lack of clarity about the postmarket regulatory controls applicable to combination products; and the lack of clarity regarding certain Agency policies, such as when applications to more than one Agency component are needed, and on the need for mutually conforming labeling for the individual components of a combination product.

FDA recognizes the need to develop policies and procedures that will ensure the efficient and effective review and regulation of combination products, and in February 2002 established a Combination Products Program within the Office of the Ombudsman to coordinate such activities. In addition to serving as a point of contact for industry and the FDA Centers on combination products issues, the Combination Products Program is developing a number of initiatives to improve the review and regulation of combination products, including developing standard operating procedures to improve the management of the intercenter review process, monitoring the progress of premarket reviews of combination products, and developing guidance on a variety of policy issues for combination products.

As one of the first steps in developing the program, the Combination Products Program staff conducted interviews of approximately 25 individuals or groups in the Center for Biologics Evaluation and Research (CBER), the Center for Drug Evaluation and Research (CDER), and the Center for Devices and Radiological Health (CDRH). The individuals or groups were recommended primarily by the Product Jurisdiction Officers in CBER, CDER and CDRH as those with significant experience in handling combination products issues. Additional individuals or groups were interviewed at the suggestion of some of the interviewees. Most of the interviewees represented the Centers' premarket review programs, but

postmarket reviewers, including those with responsibility for GMP issues and postmarket surveillance from each of the Centers were also represented.

The purpose of the interviews was to identify the combination product issues of greatest concern to FDA employees and managers, to identify areas needing policy development or revision, to solicit suggestions for improvement, and to identify (and ultimately refine and institutionalize) best practices that make the combination product review process as successful as possible.

The interviewing process was structured around a series of topics corresponding to the complete lifecycle of combination products, including product jurisdiction, intercenter consultation and collaboration, and postmarket regulation. The process was designed to elucidate the kinds of procedures, processes, or methods of communication or interaction that either significantly help or hinder the intercenter review process. FDA policy and regulatory processes were also discussed. Finally, participants were invited to comment on the roles and responsibilities of the new Combination Products Program, such as how Combination Products Program staff could best function as advocates for combination products, or as focal points for combination products for FDA employees and stakeholders.

This report summarizes the survey results and recommendations. Combination Products Program staff are also working directly with trade organizations and sponsors to obtain stakeholder views of combination products issues.

II. Survey Results

A. Consultation and Collaboration

Survey participants reported that measures critical to the success of a multi-Center review of a combination product include: timely determination that a product is indeed a combination product and requires consultation from another Center; willingness of the lead Center to engage another Center; clarity and specificity of the questions to be addressed by the consulting Center; familiarity with the other Center's regulatory authorities and limitations, timelines, jargon and culture; the degree of communication during the review process; and review management. Specific findings include:

- **Timely identification of the need for a consultative review is critical.** The sooner that recognition is made that a product is a combination product or that it will require a consultative review, the more likely it is that a consulted Center will be able to meet the timeline required for the originating Center to meet its statutory obligations. Consulted reviewers reported frustration in sometimes getting involved too late in the process (e.g., after clinical trials had been completed) to provide meaningful

feedback that the originating Center can actually use. Participants reported that, ideally, intercenter interaction on combination products should begin during the pre-submission process. Earlier identification of combination product issues was said to allow requesting reviewers more time to frame intelligent and pertinent questions to in turn assist the consulted Center in assigning the appropriate reviewers to the project, and to prevent unnecessary review work from being done. Many suggested that a separate step be added in all Centers, to screen initial submissions for potential jurisdictional and combination product issues.

- **Reviewers sometimes don't know where to send a consult request in another Center.** Some reviewers or review divisions have existing relationships with review staff in other Centers, but others report that due to differences in organizational structures and function, they view other Centers as a "black box." Sending a consulting request to the wrong division or branch can cause significant delays.

- **Consulting reviews work best when the originating Center focuses the issues and questions where input is needed.** Participants reported that some requests for consulting reviews are poorly formulated, e.g., by requesting a "drugs" or "devices" consult. A consulting request needs to be sufficiently detailed to maximize the use of the consulted Center. A related complaint is the use of jargon and technical terminology that may not be clear to another Center's review staff. On a positive note, many participants reported that they have observed significant improvement in recent years in this regard, with requesting reviewers specifying more clearly the issues that they need the consulted Center to address. Participants reported that this helps ensure that the requesting Center obtains the review input needed, avoids unnecessary duplication of effort in the consulted Center, and improves timeliness of response.

- **Combination products should be assigned to experienced reviewers. FDA employee turnover is sometimes responsible for extended review times for combination products.** Experience appears to be a primary factor in predicting a positive outcome when consultation or collaboration is required. Many of the project managers and reviewers interviewed reported that they learned through experience how to best handle intercenter reviews, but most of this knowledge is not captured in writing, not handled by current electronic tracking systems, or transferred effectively through the Centers. For example, some reviewers involved in intercenter work reported that they routinely ask sponsors for additional desk copies for consulting reviewers to minimize the need for FDA staff to photocopy substantial portions of submissions, but this practice does not appear to be widespread.

  Another area of concern to reviewers of combination products and their managers is the turnover of review staff in consulting Centers.

Mechanisms to improve review continuity would lead to higher productivity by reducing the direct and hidden costs associated with information loss and the need to reestablish roles and communication between Centers. Participants reported that this is particularly important with long-running submissions, where reviewers related experience with the other Center "changing the rules" when new staff members are assigned to the project. Creating written agreements and memoranda of understanding between Centers relative to a particular submission were suggested to help reduce the conflicts associated with new staff starting work in the middle of a product review.

- **Project managers and management must maintain an appropriate degree of managerial oversight of intercenter work.** Those involved in a significant volume of intercenter (and intracenter) work reported that it is essential for project managers and management to actively track consulting reviews to assure they are equitably and appropriately assigned and that statutory and other required timeframes are met. Some participants recommended that the Centers designate a primary contact to disseminate and track intercenter reviews. Such a process was in place several years ago, but was later eliminated when the process was decentralized in all three Centers.

  Many employees emphasized that it is important to engage another Center in a consultative or collaborative review as early in the review process as possible. Establishment of roles and responsibilities, and coordination of time requirements were reported to significantly improve the management of intercenter reviews. Participants reported that direct involvement of management from both Centers is sometimes needed to help ensure a successful outcome, particularly when the consultation is extensive or multiple review divisions from the consulting Center are involved and a harmonized Center position is needed. In general, participants reported that there appears to be less management oversight of consulting reviews than of primary work assigned to review staff. For example, some participants reported that the signoff process for consulting reviews by their managers often takes longer than for the primary review work assigned to the division.

- **Reviewers should consider recommending that sponsors provide a stand-alone section of a submission to facilitate some types of consulting reviews.** For example, CDRH reviewers conducting frequent consulting reviews for CDER and CBER reported that the information describing the device portion of the combination product is often scattered in many different sections of the submission, and that a stand-alone section of the NDA or BLA containing all device-related information would facilitate the consulting process.

- **Review staff complained that reviews often take longer when they involve consultation or collaboration between Centers.** There is a perception that consult reviews are not given the same priority in the consulted Center as the primary work that the Center normally handles, particularly if the consult is for a non-PDUFA submission. Review staff following up on the status of a consult review sometimes get the impression that the request is "not on the radar screen" of the consulted Center, and reported that multiple contacts were often required in order to receive the requested feedback.

- **Reviews that would benefit from intercenter consultation are sometimes completed entirely within a single Center because reviewers would prefer, or may feel pressure, to not consult out.** Participants cited three factors that seem to be responsible for this tendency. First, review staff from the originating Center may be personally reluctant to acknowledge the need to supplement their expertise with that from another Center. Participants cited a "do it myself" mentality throughout the Agency. Second, reviewers expressed concern about the delays caused by the consulting process, which can complicate an otherwise straightforward review. Third, perceptions about other Centers lead some review staff to think that involvement of another Center will lead to an unfair burden on the company, or an inappropriate disapproval or approval for that product. Essentially, this means a reviewer or review division may attempt to review a submission that may be partly outside their scope of competency. While this does not appear to be a common occurrence, anecdotal remarks justify it as a managerial concern.

- **Limitations in the FDA mail system sometimes have significant impact on the review of combination products.** Most participants commented on the problems associated with distributing submissions for consultation to other FDA components. Many participants related stories of late and/or lost mail and its detrimental impact on the review process. Reviewers, including senior managers, reported the need to sometimes personally deliver documents to consulting reviewers to ensure the documents were appropriately received. CDRH reported that its interactions with CBER staff at NIH were particularly hampered because the CDRH mail system does not deliver to the NIH campus. Despite an increasing awareness and use of the various special messenger or hand delivery services available within FDA, many reviewers are apparently not familiar with these services.

- **Education and cross training of combination products reviewers is needed.** First-time reviewers of combination products reported a significant learning curve in interacting with another FDA Center. Reviewers are frequently only peripherally familiar with another Center's regulatory authorities and timelines, and therefore early interactions are sometimes strained by misperceptions. Since CBER and CDER have

many similar practices and processes, including the IND process, the PDUFA program, and a number of common guidance documents, participants reported that these differences appear to be more pronounced between CDRH and the other two Centers.

For example, there appears to be a perception among some in CBER and CDER that CDRH does not review submissions “as well” or hold the sponsors to a sufficiently high standard for demonstration of safety and effectiveness. Some CBER and CDER participants mistakenly suggested that CDRH does not require effectiveness data, and that the PMA process was required only for the first device of a kind (i.e., the second of a kind could be regulated under the 510(k) process). Several CDRH reviewers reported feeling dismissed or being treated in a condescending manner when dealing with some CBER and CDER staff members. On the other hand, CDRH staff reported feeling frustrated in not getting sufficient or timely feedback from CBER and CDER consultants on IDE submissions, where CDRH is required to provide a complete response on all aspects of the application within 30 days of receipt.

Differences in policies and perspectives also complicate the review of combination products. For example, in reviewing the safety and effectiveness of “fixed-combination prescription drug products” (where two or more drugs are combined in a single dosage form), CDER requires the contribution of each active ingredient in the combination to be demonstrated. Therefore, CDER participants reported a tendency to apply a similar approach to combinations of drugs and devices or drugs and biologics. In contrast, CDRH generally reviews the safety and effectiveness of the overall combination product without requiring the contribution of the components to be separately evaluated.

Participants reported that cultural differences between each of the Centers affect their ways of doing business and of interacting internally and with sponsors, which can cause some conflicts when consulting or collaborating with other Centers on combination product reviews. For example, CBER and CDER rely extensively on regulatory project managers to manage interactions internally and with sponsors, but CDRH relies on its lead reviewers for many of these responsibilities. Also, where CBER or CDER sometimes see CDRH as applying a lower standard for the demonstration of safety and effectiveness, CDRH staff reported its methods were less burdensome and more likely to help bring valuable medical products to market faster.

Participants suggested that cross training and education would not only improve the understanding of combination products reviewers of the regulations and practices of different Centers, but would also encourage the transfer of information related to best practices and help to develop and update contact lists for the times when intercenter collaboration and coordination is required. For example, adverse event reviewers in CDER

and CDRH are now sharing contact lists and planning joint seminars to facilitate intercenter interaction, which may help the Agency more quickly respond to adverse events for drug-device combination products.

Some participants recommended that the Combination Products Program develop a "welcome package" that could be provided to review staff upon the assignment of a combination product review. Such information could include background on the various regulatory authorities and timelines of the Centers, points of contact for each Center for various issues, and best practices in interacting on combination products reviews.

- **Ongoing communication is key to sustaining a consulting relationship.** Consultants reported that the review of combination products goes best when they feel a part of the lead Center's review team. Inclusion in meetings with sponsors, early notification of upcoming submissions, status of sponsor responses, copies of correspondence to sponsors, and similar methods of communication all contribute to investing the consulting reviewer in the process. In turn, consulting reviewers reported that with the establishment of such a relationship, intercenter interactions became less formal, with greater likelihood to share consulting review findings prior to final signoff, leading to a faster and more productive overall review process. Participants reported that communication is particularly important when the lead Center chooses not to utilize some of the recommendations provided by the consulting reviewer. To minimize the ramifications of consultants feeling like they had "wasted their time," several employees suggested that it is important for the originating Center to effectively communicate its position to the consulting Center so that an effective consulting relationship is maintained.

  Aside from good communication and review management on specific applications, some groups with analogous (generally clinically focused) responsibilities reported the existence of excellent relationships with their counterparts in another Center. Such relationships include more regular and informal consultations, joint seminars or rounds, establishment of common efficacy endpoints, and other factors necessary for establishing a shared vision and common approach to similar issues. Participants from these and other groups suggested that FDA be reorganized along clinical lines to promote such interaction. For example, a pilot review Office responsible for all FDA regulated cancer therapies, ophthalmic products, or medical imaging products could be established.

B. Product Jurisdiction

A number of issues were raised regarding the methods FDA uses to assign a lead Center to review a combination product. These issues addressed the division of labor among the Centers, the Intercenter Agreements, the Request for Designation (RFD) process, and the role of front-line reviewers and project managers in product jurisdiction. Specific findings included:

- **The current jurisdictional agreements among the Centers need a fresh look. The Intercenter Agreements are outdated and being pushed to their limits.** The current Intercenter Agreements differ in format and scope. Some of the guidance is categorical relative to certain product classes, while others focus on providing jurisdictional principles between Centers. Combination product jurisdiction decisions statutorily require a determination of the product's "primary mode of action," a term which is not defined in the statute or regulations.

  For some products of a given type, based on the information available at the time of assignment, the primary mode of action may be attributed to a component regulated by one Center, while for other products in the same general class, the primary mode of action may be attributable to a component that is normally regulated by another Center. As a result, the review jurisdiction for different products within a given class may be split between two Centers, leading to differences in the application of premarket regulatory authorities, review policies, postmarket regulatory controls, and other factors relevant to product regulation. Senior managers interviewed reported that the lack of clear Agency policy on the jurisdiction for certain product classes makes the Centers reluctant to invest in hiring, training, guidance development and standards activities for products they may not be regulating in the near future.

  Interview participants reported that jurisdictional decision making sometimes appears to be arbitrary, and that class-wide jurisdictional assignments should be made whenever possible. Some participants reported that they believe that their Center should have jurisdiction over all combination products incorporating a component that would independently be reviewed by that Center.

- **Front-line review staff and project managers have a critical role in product jurisdiction and the assignment of combination products.** Most combination products are not officially submitted to FDA for assignment as part of the Request for Designation (RFD) Process described in 21 CFR Part 3. In many cases, review staff reported using the guidance provided by the Intercenter Agreements or discussing the product with their Center's Product Jurisdiction Officer to determine whether a product should be appropriately reviewed in that Center. On the other hand, participants also reported instances where such consultation about jurisdiction did not occur. Such decisions often set precedent, so participants emphasized that it is critical that front-line staff be alert to jurisdiction and combination products issues, and contact their Center's Product Jurisdiction Officer for guidance when appropriate.

- **The Request for Designation (RFD) Process is generally viewed as an effective approach to establish jurisdiction for a combination product, but communication could be improved.** Participants generally reported positive experience with the RFD process used to assign a lead Center for combination products. As noted above, some participants expressed concern with the perceived arbitrariness of some decisions. Several participants raised issues regarding the roles and responsibilities of the individuals involved in the RFD process, and the timelines for response. For example, Centers are requested to provide input to the FDA Ombudsman's Office within 21 days of receipt of the RFD, but some reviewers reported being given 30 or more days by their Center's Product Jurisdiction Officer to review and recommend the designation. Others reported that they were not consistently consulted by their Center's Product Jurisdiction Officer on RFD's involving their product area expertise, or that they received excerpts of the RFD rather than the full submission. Some participants recommended that a database of RFD decisions be made available to FDA employees that would allow review staff to be aware of the reasoning behind the various decisions. Finally, most participants reported that the jurisdictional decision, including the final RFD response letter, should be communicated to those providing input to the RFD process.

C. Postmarket Regulation Issues

Combination products sometime raise unique concerns about safety and effectiveness, or risks to the public health, arising specifically from the combination nature of the product. The statute permits the Agency to draw from the statutory and regulatory authorities applicable to all components of the combination product in order to ensure adequate demonstration of the safety and effectiveness of a product. For example, a drug-coated device may be subject to the device Quality Systems Regulation for the device component, to drug Good

Manufacturing Practices (GMP's) for the drug coating, and to a mix of requirements, as appropriate, for the combined product.

While this flexibility may be appropriate to enable FDA to best promote and protect public health and address unique issues arising from the combination of two products that would otherwise be separately regulated, some complained that there is a lack of consistency in the application of postmarket requirements for such products. Since manufacturers must design their manufacturing and quality systems to address the types of products they produce, a sponsor that primarily manufacturers devices, for example, may not have the systems in place to manufacture a drug-coated device that will be subject to drug GMP's. Similarly, product sponsors have separately reported confusion in deciding which adverse event monitoring regulations to follow for a combination product, and that reporting to multiple Centers has been required in some cases, which they believe is duplicative and unnecessary.

- **Post-marketing divisions and ORA sometimes have difficulty in assessing which Center has responsibility in responding to adverse events or in conducting compliance inspections for combination products.** Most participants stated that the premarket regulatory route generally dictates which postmarket controls would be required for a combination product. GMP reviewers from CBER, CDER and CDRH generally reported that their Center's GMP regulations were sufficiently flexible to apply to combination products, although CBER expressed concern over the adequacy of CDRH's Quality Systems Regulation to address biologic components (such as cellular products) used in the manufacture of a finished product. Conversely, some sponsors have separately complained that drug GMP's are inadequate to address complex drug delivery systems (some of which may be assigned to CDER), and that such products should instead be subject to the Quality Systems Regulations typically applied to medical devices. Current efforts in coordinating GMP inspections and clarifying specific requirements for companies that produce combination products appear to be conducted on an ad-hoc basis.

  While CBER and CDER have established relationships (including a common set of controlling regulations) between postmarket surveillance reviewers, participants reported that similar links with CDRH do not exist. As a result, CDRH adverse event reviewers reported that considerable "fumbling around" sometimes occurs in determining jurisdiction and/or engaging a consultant from CBER or CDER when a combination product issue emerges.

D. Electronic Submission Tracking Systems

Each Center has information technology systems to automate the tracking functions required for review management. As would be expected, each system is tailored to the regulatory framework that governs the majority of that Center's

work. Some Centers have multiple systems tracking data based on the type of application or submission. These systems were largely developed independently, are not on the same computer platforms, and capture different kinds of data. The current tracking systems are generally not designed to capture consulting reviews. There is also a lack of uniformity, even between review divisions within a Center, in how intercenter consulting reviews are tracked.

- **None of the Centers' tracking systems currently identifies whether a product is a combination product, or the status of consultation with another Center.** When questioned about the limitations of current tracking systems, many participants reported that a simple "flag" that a product is a combination product and/or requires intercenter consultation could allow for a tracking and reporting function, or determination of review metrics specifically for combination products. These needs were not anticipated when these systems were developed. With increased awareness of the potential benefit that computer systems could add to the management of combination product reviews, additions and upgrades such as this are being considered at all Centers. In fact, such changes might be required if pending legislation is enacted calling for FDA reporting of review metrics for combination products.

- **Centralized monitoring, but not assignment or signoff, of combination products submissions would be desirable.** A number of participants expressed the need for a centralized method of oversight as a means to help ensure that consulting Centers meet the time frames requested by the originating Center. On the other hand, several participants cautioned that adding another level of oversight would be burdensome and that the addition of new steps or layers in the assignment or signoff process would slow down an already complex process.

III. Recommendations and Summary

A variety of themes emerged from the interview process that helped to further refine the current focus of the Combination Products Program. Based on the survey results, and the initial input received from stakeholders (including trade associations such as AdvaMed), the Program is beginning to develop and implement a number of initiatives. It is expected that these initiatives will be even further refined as input is received from meetings with stakeholders and the public meeting described below. On July 12, 2002, the FDA Deputy Commissioner called for each Center and the Office of Chief Counsel to nominate a senior representative to serve on a steering committee to guide these efforts. The overall goal is to improve the regulation of combination products and

to facilitate intercenter interaction without adding unnecessary layers of management or oversight. Specific recommendations emerging from, or already underway but further validated by, this survey include:

A. Meeting with Stakeholders

- Continue to meet with stakeholders, both within and outside the Agency, to identify areas needing policy development or revision and to identify (and ultimately institutionalize) best practices. In addition to the approximately 25 interviews of FDA employees that are the subject of this report, Combination Products Program staff members have met several times with AdvaMed members, and similar meetings with PhRMA and BIO are being planned.

- Hold a public meeting in the Fall of 2002 to obtain stakeholder input on a variety of combination products issues, including the definition of "primary mode of action" and related jurisdictional issues, when dual marketing applications are needed for a combination product, and postmarket requirements for combination products.

B. Development of Review Programs, Policies, Processes

A major focus of the Combination Products Program is to develop review programs, policies and processes to facilitate the review of combination products or other projects requiring intercenter consultation or collaboration. The first major effort was to develop with CBER, CDER and CDRH a Standard Operating Procedure (SOP) on Intercenter Consultation and Collaboration. The SOP is in effect as of July 31, 2002.

The SOP outlines a number of policy and procedural issues directly related to the "best practices" identified in the interview process. Elements of the SOP that relate to the survey results include: the Agency's policy that "consults count," with accountability of consulting Centers to meet established deadlines; identifying the need for consultation as early in the review process as possible; providing methods to determine who in the consulting Center will conduct the consulting review; identifying specific questions and issues to be addressed by the consulting review team; providing for ongoing communication between the originating Center and the consulting Center during the review process; providing for management oversight of the consulting review process; and outlining methods to improve logistical handling of consulting reviews. The SOP is intended to be a "living document" and a future draft is already planned to further detail the collaborative review process. Related recommendations include:

- Work with the training components in CBER, CDER and CDRH to develop appropriate educational and cross training programs for reviewers of

combination products and their managers. Such programs would address the issues identified during the interview process, such as the lack of familiarity of FDA staff with the regulatory authorities/limitations, policies, timelines, organizational structures, etc., of other Centers. In addition, combination products reviewers would benefit from training in the statutory, regulatory and policy issues surrounding combination products and jurisdiction. Some participants suggested that a "welcome package" be provided to review staff upon the assignment of a combination product review that would include such information, as well as "helpful hints," "lessons learned," and best practices.

- Explore methods to streamline the distribution of regulatory submissions for consultation by another Center. Most participants commented on the problems associated with distributing submissions for consultation to other FDA components. Improving awareness and use of the special messenger or hand delivery systems available in the three Centers should help in this regard. Further work is also needed to explore whether the Centers' utilization of Master Files or similar mechanisms could be improved to reduce the need for duplicative review work for delivery systems and similar products assigned to multiple review divisions.

C. Review Process Monitoring

One of the functions of the Combination Products Program is to monitor and provide oversight of the progress of premarket reviews of combination products, and to help identify and resolve issues arising during the review process. Implementation of this function is currently limited by the lack of appropriate "flags" in the Center tracking systems to identify whether a product is a combination product and/or whether it is subject to intercenter consultation or collaboration. For example, currently it is not possible to run a report identifying all combination products under review in the Agency, or even within a single Center.

- Combination Products Program staff are working with review management representatives from CBER, CDER and CDRH to implement an interim method of tracking of combination product reviews while the formal tracking systems are being developed. Note that enactment of HR 3580 or similar legislation would likely require the tracking and annual reporting of review metrics for combination products.

D. Guidance and Transparency

Another function of the Combination Products Program is to develop guidance for FDA reviewers and industry on a number of key issues where there is a lack of clarity or transparency. In addition to establishing a combination products page

on FDA's Internet site, FDA has begun posting a series of "jurisdictional updates" to communicate recent jurisdictional decisions to the regulated community. These updates are intended to provide greater transparency and currency to the jurisdictional process. Other areas cited in the interviews where guidance development is recommended are cited below. A high-level FDA steering committee is being formed to guide these efforts:

- Regulatory authorities. Better guidance is needed to more consistently assess which set of premarket regulatory authorities is best suited for a given type of combination product.

- Dual submissions. Guidance is needed to determine when a combination product must be subject to marketing applications for each of its components to demonstrate safety and effectiveness, or when a single application would suffice.

- Postmarket requirements, such as GMP's and adverse event reporting. Guidance is needed to better identify which postmarket controls (potentially including a hybrid of existing authorities where appropriate) will apply to combination products.

- Cross labeling. Better guidance is needed to determine the circumstances under which the labeling of an already approved product must be changed to reflect its use with another regulated product.

- Guidance for combination product sponsors on how best to organize their applications for intercenter review. For example, a stand-alone "device section" might facilitate consultative review by CDRH for a combination product BLA or NDA reviewed by CBER or CDER.

- Jurisdiction and Intercenter Agreements. Participants recommended several areas where development or revision of jurisdictional guidance is needed:

    - Revision of the Intercenter Agreements. Participants cited the lack of consistency in format and scope of the three existing Agreements, the outdated examples, and in some cases, the inconsistency of the Agreements with the "primary mode of action" as reasons that revision of the Agreements are urgently needed. Some participants recommended that the Agency develop a single jurisdictional guidance document, rather than the current Intercenter Agreement approach.

    - Definition and interpretation of "primary mode of action." Participants expressed the view that better guidance would improve consistency and transparency and reduce the "turf battles" between Centers that seem to repeatedly surface as new jurisdictional decisions are needed.

- Methods to better communicate the basis of RFD decisions within FDA and to stakeholders.

E. Focal Point and Advocacy

The Combination Products Program is designed to serve as a focal point for combination products issues for stakeholders and FDA employees. Program staff members are working on a variety of projects as requested by stakeholders or internally to help facilitate intercenter interaction. Continued education and outreach is needed to inform stakeholders and FDA employees about this function of the Combination Products Program.