CPC COMBINATION PRODUCT COALITION

INCREASING FOCUS ON COMBINATION PRODUCTS

June 8, 2009

I. EXECUTIVE SUMMARY

Combination products[1] increasingly incorporate cutting-edge, novel technologies that hold great promise for advancing patient care. Patients have already seen the benefit of combination products in therapeutic areas such as oncology, cardiology, neurological and metabolic disorders, and several other areas. Further, the explosion of new technologies such as nanotechnology, health information technology, molecular diagnostics, and cellular and tissue engineering are expected to bring even more products to the forefront. While these innovative combinations have the potential to make treatments safer, more effective, and more convenient or acceptable to patients, they also entail the interaction and resolution of the different regulatory paradigms under which the separate products are governed.

Further, the combination products industry has grown, and is expected to continue to grow, at a rapid pace. The impact on the Agency's workload will very likely be proportional to this growth.

Thus far, FDA's Office of Combination Products (OCP) has dealt well with the challenges this growth presents, for example, by responding timely to regulatory submissions. The Office has also maintained an air of transparency, openness, and desire for input. At the same time, the Agency's increasing burdens has left little time for focusing on combination product policy development, both within OCP and throughout the Centers and the Office of the Commissioner.

More than ever before, combination product manufacturers require predictability and flexibility in order to navigate the regulatory complexities that combination products raise. While industry has indicated its needs in several areas, the needs are particularly acute with respect to:

1. Good Manufacturing Practices (GMPs) applicable to combination products
2. Clinical trials on combination products
3. Post-approval product modification issues.

As we enter this new era that presents exciting opportunities for health care, we urge the Agency not to lose focus on combination products, but rather to ensure continued, much-needed combination product policy development and access to Agency personnel.

[1] For purposes of this paper, the definition of a "combination product" is the same as in 21 CFR § 3.2(e) -- 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.

II. PUBLIC HEALTH IMPORTANCE

Combination products represent some of today's most promising areas in advancing patient care. There are numerous drivers of these technologies, the principle one being the broad need and desire for enhanced outcomes in safety and effectiveness. For example, combination products often enable the use of therapy candidates that cannot be used alone due to systemic effects and toxicities. Combination product technology can also enable safer and more effective technologies due to local administration and individualized therapy. These and other drivers have paved the way for combination products that help patients suffering from cancer, heart disease, multiple sclerosis, cerebral palsy, spinal cord injuries, rheumatoid arthritis, diabetes and other serious diseases and conditions.

Part of the reason combination products offer such promise is that they often utilize some of the most cutting-edge scientific technologies – nanotechnology, genomics, molecular diagnostics, tissue engineering, stem cell research, and more. In addition to these technologies, the "mere" convergence of regulated articles fosters novel approaches to treatment and diagnosis – the combinations allow the best of all worlds to confront today's health problems.

The opportunities for advancing health care are perhaps best demonstrated by a few examples. Of course, the classic example of a combination product that revolutionized patient care is the drug-eluting stent. In addition, consider these examples of combination products that are being researched, are under development, or are currently on the market that demonstrate the potential for advancement in patient care:

- Magnetic nanoscopic probes that can locate tumors and attach to cancer cells, and that have the potential to carry and deliver drugs to treat those cancerous cells.[2]

- A miniscule device put in the eye to provide controlled and sustained release of a variety of drug compounds to treat diabetic macular edema and age-related macular degeneration.[3]

- A small hand-held device that allows drugs to be easily inhaled, enabling rapid treatment of migraines, cancer pain, or schizophrenia without injections or slow-acting capsules.[4]

- Small drug-eluting stents implanted into airways as a minimally-invasive treatment option for emphysema.[5]

- Using autologous stem cell therapy and a delivery device to treat cardiovascular disease.[6]

---

[2] Medical Device Link, Device Talk Blog, *Nanoprobes Hunt Down Cancer Cells*, http://www.devicelink.com/mddi/blog/?p=981 (last accessed Apr. 13, 2009).
[3] http://www.surmodics.com/applications-ophthalmology.html
[4] http://www.alexza.com/about/the-staccato-system
[5] http://broncus.com/

- A metal device packed with bone growth material that fosters natural bone regeneration, which can replace traditional, painful bone grafting procedures.

- Light-activated drugs (photosensitizers) administered by IV injection to treat a range of diseases characterized by rapidly growing tissue, including the formation of abnormal blood vessels, such as cancer and age-related macular degeneration.[7]

There are many more out there, and many more to come.

III. INDUSTRY SIZE AND GROWTH

Quantitative industry estimates reflect this growth and development and the opportunities in this area. In terms of the industry as a whole, in 2005, the combination products market was estimated at $6.4 billion and expected to reach $11.4 billion by 2010.[8] Further, some sources estimate that 30% of new products under development are combination products.

The numbers on individual segments are also staggering. As of mid-2006, 130 nanotech-based drugs and delivery systems and 125 devices or diagnostic tests were in preclinical, clinical or commercial development, and the U.S. National Science Foundation has predicated that nanotechnology will produce half of the pharmaceutical industry product line for 2015. Further, recently the United States' demand for nanomedicines was forecasted to expand annually by 17%, reaching $43 billion in 2012 and $85 billion by 2017. Therapeutic monoclonal antibodies are expected to comprise a significant portion of the nanomedicine market, as over 1/3 of biotechnology development projects are seeking to apply those proteins to treat a wide array of conditions. That sector alone is expected to reach $31 billion in 2012. Other major nanomedicine market segments include polymer-based drugs and crystalline nanomedicines.[9]

By the Agency's own measure, in 1990, we saw 1,000 scientific publications and 200 patent applications filed related to nanotechnology. By 2002, those numbers had increased to over 22,000 publications and 1,900 patents. As FDA recognized, "This exponential increase in scientific publications and patents is the result of increased discovery and investment in nanotechnology that will likely result in substantial and continual changes in products falling under the regulatory authority of the FDA."[10]

Without a doubt, this growth will impact the Agency. Indeed, FDA has acknowledged that these increases in the discovery, research, and marketing of combination products has and

---

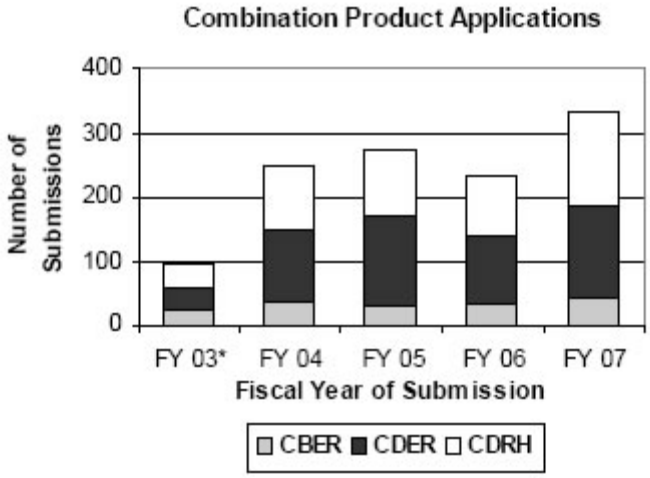
[6] http://www.bioheartinc.com/product.php
[7] http://www.qltinc.com/Qltinc/main/mainpages.cfm?InternetPageID=216
[8] BCC Research, Drug-Device Combinations (June 2005) (obtained from MaRS Venture Group, Emerging Technology Brief (Sept. 2006)).
[9] Drug Delivery Technology, *Nanomedicine in a Nanominute: A Market Brief*, Vol. 9, No. 3 (Mar. 2009).
[10] FDA, Nanotechnology: A Report of the U.S. Food and Drug Administration Nanotechnology Task Force (Jul. 25, 2007).

will continue to substantially impact the types and numbers of products falling under the FDA's regulatory authority:

> Since combination products involve components (biologics, drugs, and/or devices) that would normally be regulated under different types of regulatory authorities, and frequently by different FDA Centers, they also raise challenging regulatory, policy, and review management issues. The differences in regulatory pathways for each component can impact the regulatory processes of all aspects of the product life cycle, including preclinical testing, clinical investigation, marketing applications, manufacturing and quality control, adverse event reporting, promotion and advertising, and post-approval modifications. In addition, combination products increasingly use state-of-the-art, innovative technologies that challenge existing regulatory and scientific knowledge.[11]

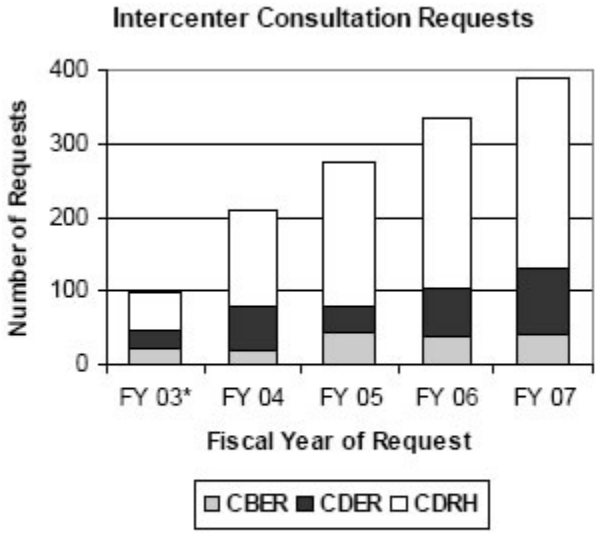
Quantitative FDA data evidence this trend. For example, the most recently published performance report from the FDA's Office of Combination Products (OCP) shows that three key combination product-related activities have steadily climbed, reaching their highest point since OCP's inception in 2002. In particular:[12]

- **The number of combination products submitted for review reached a 5-year high in FY 2007 and increased by 42 percent from FY 2006 (235) to FY 2007 (333) (see graph below).**



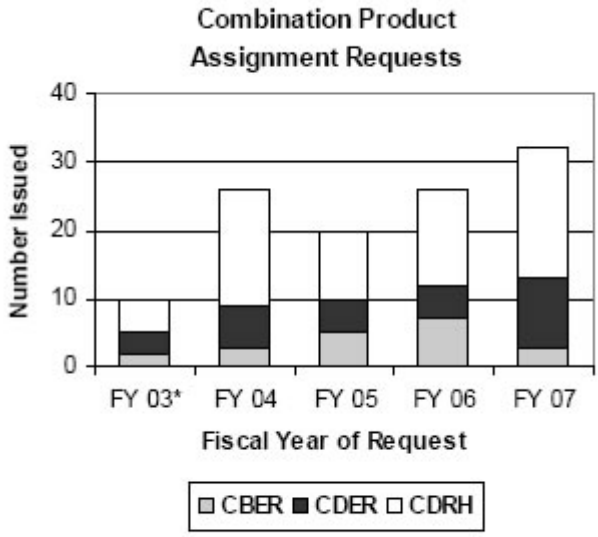
[11] OCP Annual Report FY 2007.
[12] *Id.*

- **The number of intercenter consultation requests on combination products increased by 16 percent from FY 2006 (335) to FY 2007 (390), reaching a 5-year high (see graph below).**



** Numbers do not represent all of FY 2003. FDA began data collection on April 1, 2003.*

- **The number of assignment requests issued increased by 23 percent from FY 2006 (26) to FY 2007 (32), reaching a 5-year high.**



** Numbers do not represent all of FY 2003. FDA began data collection on April 1, 2003.*

The Agency has already been significantly impacted by the increasing development and marketing of combination products, and this impact can only be expected to increase.

IV. IMPACT ON THE OFFICE OF COMBINATION PRODUCTS AND THROUGHOUT AGENCY

The OCP has dealt with these significant increases submissions well. In particular, the Office has been able to maintain timeliness in its responses and has continued to move the regulatory decision-making process forward effectively. For example, in responding to Requests for Designation ("RFDs"), the Office has not only consistently met the 60-day statutory timeframe, but has often exceeded it.[13] Further, the OCP has consistently facilitated timely premarket review in accordance with the performance goals established under PDUFA and MDUFMA.[14]

Just as important, the OCP has preserved a sense of openness and transparency in its policy development activities, goals, and initiatives. For instance, the OCP has done numerous speaking engagements over the years and has participated in a number of combination product seminars and conferences, such as the FDA/DIA Cross Labeling Workshop and the RAPS/CPC Summit on Combination Product Issues. As another example, the Office has often encouraged those who are uncertain about how an issue should be handled for their particular combination product to come to the OCP for assistance. We have also found the product-specific information the OCP posts on its website, for example concerning product jurisdiction issues, to be extremely helpful.

Further, the OCP has continually evidenced a willingness to solicit and consider public input as it engages in policy development. For example, the Office proactively posted concept papers on adverse event reporting for combination products and on marketing applications for combination products. By the OCP's own description, the papers were posted with an intent to "stimulate public input" and obtain comments on "the general direction outlined, on alternative approaches that you believe FDA should consider, on the mechanisms you believe are needed for implementation (e.g., guidance, regulation), and on any other issues that you believe should be addressed in future guidance and/or regulations on these issues." This approach to policy-making has helped foster thoughtful and informative Agency guidance documents and policies.

These successes and initiatives are particularly commendable when one considers that, in spite of the tremendous industry growth and consequent impact on the Agency, the resources FDA has been able to devote to combination products has remained nearly static. Indeed, the first annual report of the OCP reported that the Office was staffed by six individuals, with one vacancy. At that time, the eventual projected staff was ten individuals. Today, five and a half years later, there is just one more staff member.[15] The OCP has seen sharp increases in its workload without much of an increase in its capacity. Combination product resources are also needed elsewhere in the Agency, including at the individual Centers and in the Office of the Chief Counsel to work with the OCP.

---

[13] *See e.g.*, OCP FY 2007 Annual Report.
[14] *Id.*
[15] See FDA, *Frequently Asked Questions About Combination Products, available at:* http://www.fda.gov/CombinationProducts/AboutCombinationProducts/ucm101496.htm (last accessed June 8, 2009) (stating: "The Office of Combination Products currently has 7 staff members.")

At the same time, we should note that the issue is not just money, but structural dedication and prioritization. Each of the involved offices needs to place a high enough priority on combination products to accomplish the needed policy-making goals. In this regard, we suggest that dedicated combination product liaisons within the Centers and at the Office of the Chief Counsel be indentified and directed to participate in combination product policy-making.

In summary, in the face of sustained growth in the combination products area, although the agency has continued to address individual regulatory submissions in a timely and effective manner, progress on policy development initiatives has slowed, including in important areas like GMPs, clinical research, and post-market product modification issues.

V. REGULATORY NEEDS

To enable patient access to innovative products, manufacturers need clarity and predictability on important policy development issues. Without a doubt, one of the biggest concerns of an FDA-regulated manufacturer is regulatory compliance. Manufacturers want to comply with FDA regulations that apply to them for a variety of reasons, not the least of which is that a high level of compliance helps to ensure a high quality product that health professionals and patients can use safely and reliably. In order to achieve a high level of compliance, though, manufacturers must first thoroughly understand how the regulations apply to them. Understandably, when cutting-edge technologies are concerned, the application of existing regulations and standards can be unclear or even downright confusing. This lack of clarity affects manufacturers in a very real way. A survey that our organization conducted on the need for guidance in the combination product area illustrates this effect.

A. Purpose

In late 2007, our organization began to plan its 2008 advocacy agenda. As it did, our diverse group of member companies identified a need to step back and take the industry's pulse on existing combination product policies and guidance. The organization's goal in doing so was to ensure that it remained focused on its mission of developing and advocating improved policy positions on regulatory issues affecting combination products, which necessarily cut across multiple diverse industries. With that goal in mind, the CPC members developed and sponsored an online survey designed to gauge industry priorities for guidance and rulemaking activities in the realm of combination products.[16]

B. Scope

The CPC survey evaluated participating manufacturers' demographics, their satisfaction with existing combination product regulatory guidance, and their opinions as to topics on which more or better guidance is needed. Participants ranked potential regulatory guidance topics according to perceived importance and then answered questions related to the type of guidance they would like to see and why they thought such guidance was needed.

[16] The survey was conducted with the assistance of the Regulatory Affairs Professionals Society's survey software.

C. Methodology

The survey was distributed widely among pharmaceutical, medical device, and biologics manufacturers, with the help of several trade groups and industry publications. Respondents completing the online survey were allowed to remain anonymous, although they could submit optional identifying information. To avoid having a single company or industry segment disproportionately represented, respondents were asked to complete only one survey per organization. Individuals completing the survey were asked to collaborate with colleagues at their company to provide a comprehensive view of their organizations' activities.

D. Demographics

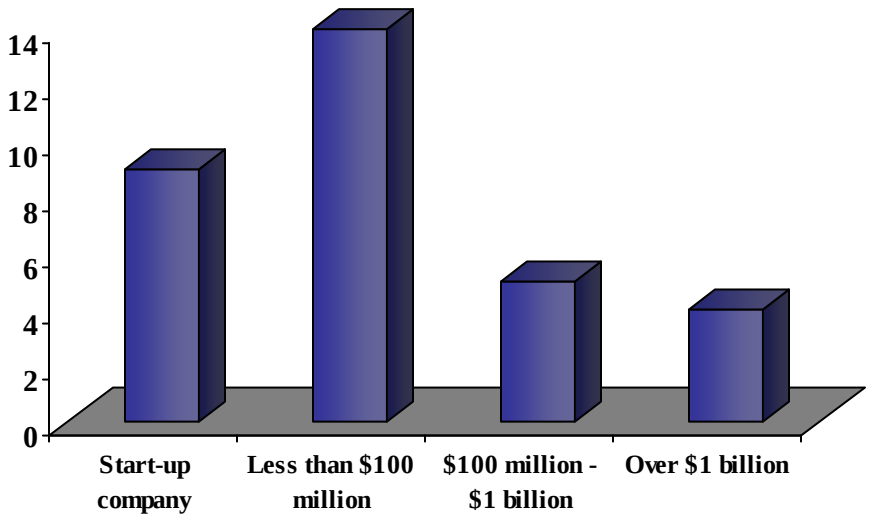
(1) Primary Product Focus

The medtech sector was particularly well-represented among survey respondents, with 78% of the survey's 32 total participants indicating that their primary product focus was medical devices. Five of the 32 companies (16%) indicated that their primary product focus was pharmaceuticals, while only two companies (6%) said that biological products were their primary product focus.

(2) Company Size – Annual U.S. Sales

Survey respondents represented a wide range of sizes—from start-up companies to manufacturers with more than $1 billion in annual domestic combination product sales. However, the majority of respondents indicated they either were start-up companies or had less than $100 million in annual U.S. sales of combination products—which is not surprising given the relatively recent advent of the combination product industry.

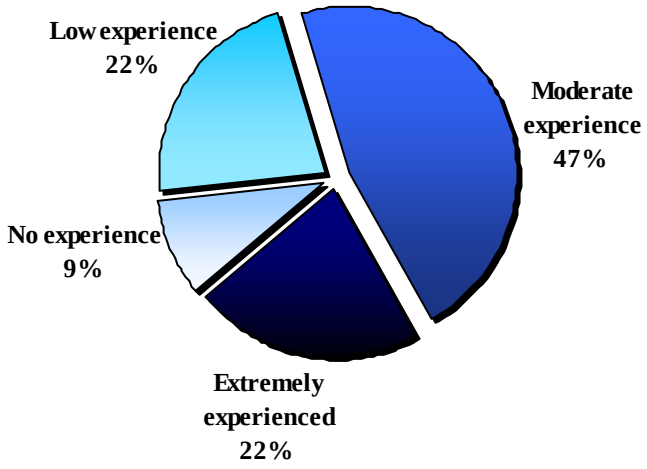
Annual U.S. Sales of Combination Products



(3) Combination Product Experience

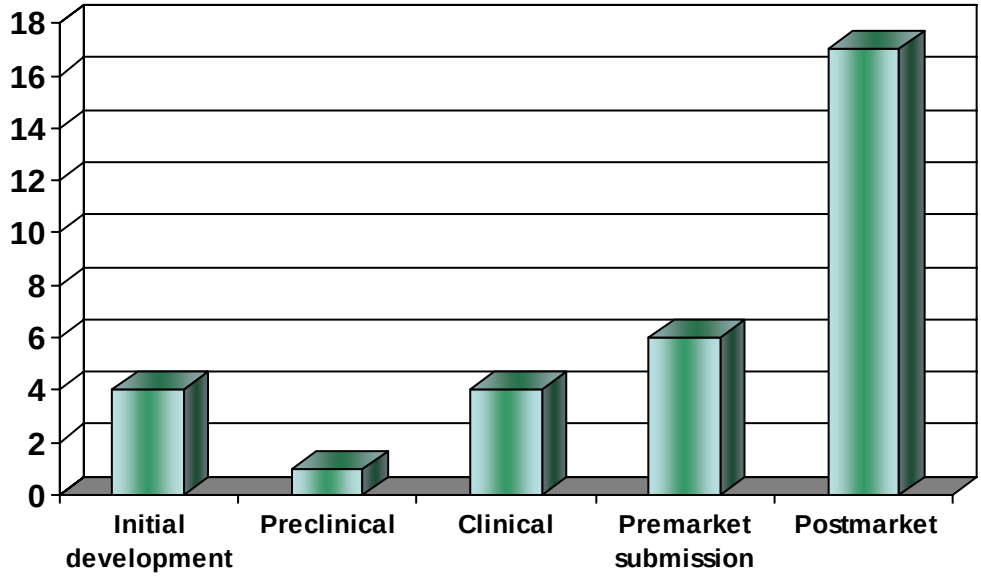
In order to stratify responses by experience level, the survey asked respondents about their familiarity with developing and commercializing combination products. Participants were asked to rate their experience on a scale from no experience to extremely experienced. Nearly half (47%) said they had a moderate level of experience with combination products, which was defined as having commercialized, developed, or licensed and marketed at least one combination product. Slightly less than a quarter of respondents (22%) said they had low experience, and another 22% described themselves as extremely experienced. Low experience was defined as having one or more combination products in the beginning stages of development. Extremely experienced was defined as having commercialized, developed, or licensed and marketed several combination products. Only three survey participants (9%) said they had no experience at all with developing or commercializing combination products.

Combination Product Experience



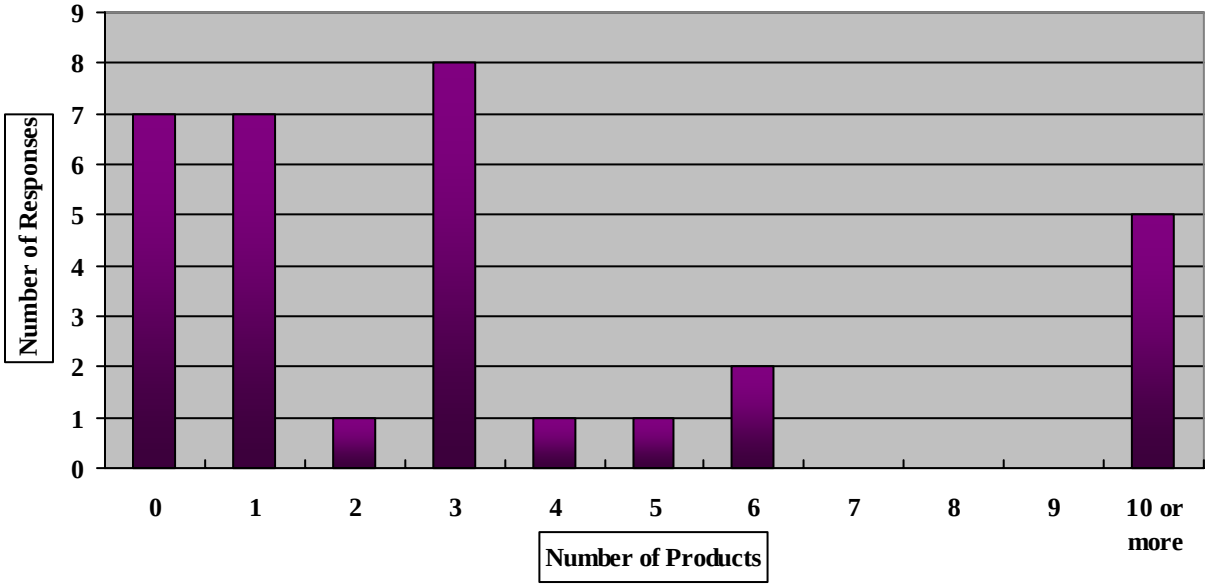
The survey asked respondents to indicate the stage of their most-developed combination product. The majority of respondents had at least one product in the postmarket stage. However, every stage of development was represented among respondents.

Stage of Development of Combination Product Furthest Along



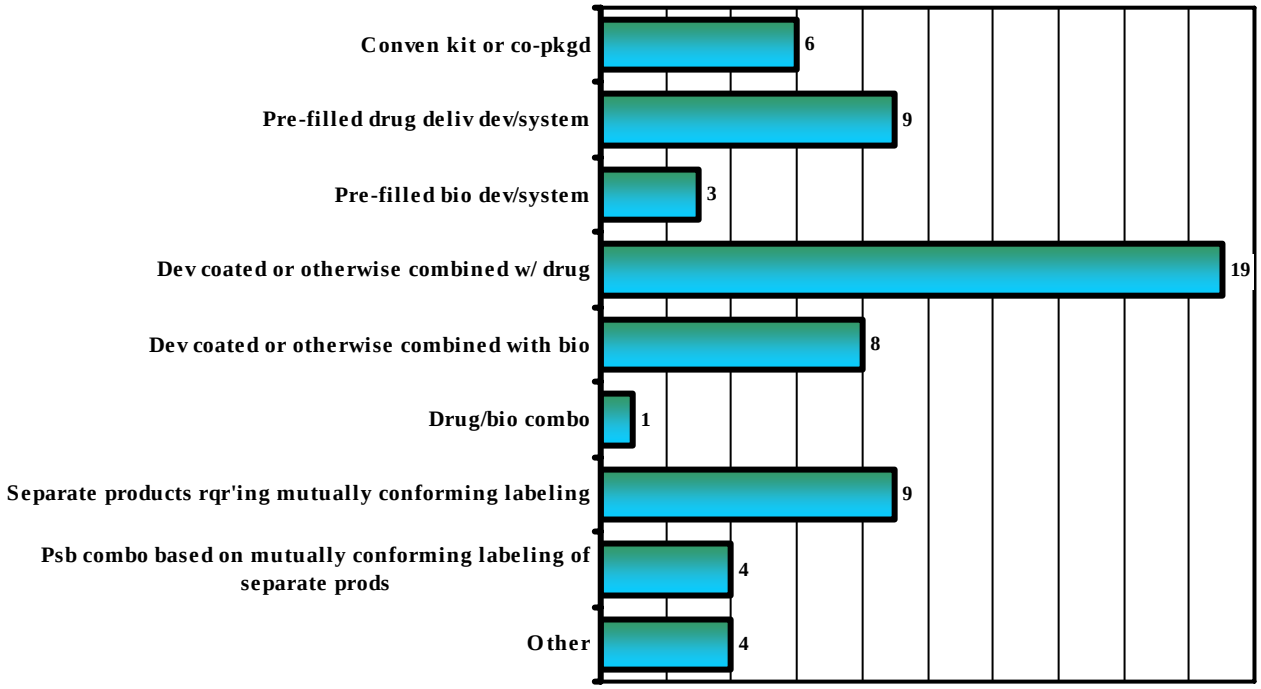
Also, the survey gauged companies in regard to the total number of combination products that they had developed and brought to market. The majority of respondents had produced between zero and three products, although five companies indicated that they had more than 10 combination products on the market.

Number of Products Developed and Brought to Market



The survey also required companies to categorize their combination products in the same way that OCP categorizes them. Respondents were allowed to select as many categories as needed. The majority of respondents indicated that they were developing a combination product composed of a device that is coated or otherwise combined with a drug. Other top responses included prefilled drug-delivery devices or systems, devices coated or otherwise combined with a biological product, and cross-labeled products. The large number of products with device components is not surprising given the number of medtech companies completing the survey. Also, the types of products represented in the survey were generally proportionate to the number and type of combination products that undergo FDA review.

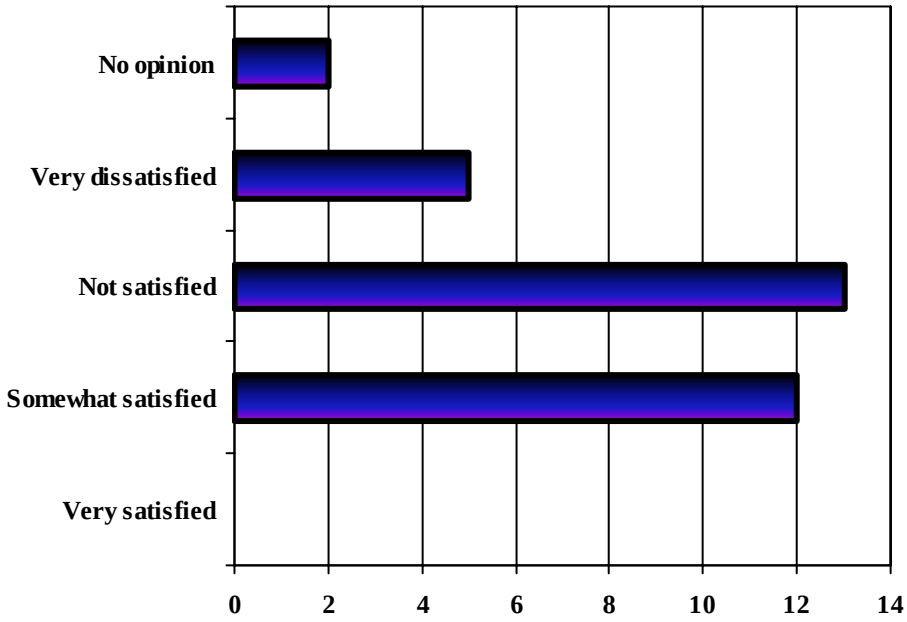
Types of Combination Products Developing or Currently Marketing



E. Satisfaction with Existing Guidance

The second major section of the survey inquired about respondents' satisfaction with existing guidance sources, including both FDA and non-FDA sources, such as trade associations, consultants, and legal counsel. The latter sources were included as means of assessing the totality of existing guidance. Just over half of the respondents (56%) indicated some level of dissatisfaction with existing guidance. Twelve of the 32 participants said they were somewhat satisfied with existing guidance.

Satisfaction with FDA and Non-FDA Guidance



Satisfaction seemed somewhat to be linked to experience in the industry, as all three participants who said they had no experience with combination products indicated they were unsatisfied with existing guidance, and just one of the six respondents at the premarket submission level of product development indicated any level of satisfaction. In addition, only one of the five pharmaceutical companies said they were satisfied with existing guidance.

On a more granular level, some respondents offered additional comments about their satisfaction with existing guidance. For example, one respondent commented on the need for additional detail in FDA guidance, noting that "part of the problem with existing guidance documents is that they are at the 40,000-foot level, and there needs to be more guidance at the 10,000-foot level." Other respondents commented on specific areas where they were dissatisfied with existing guidance, such as device change control issues and the lack of detail on how pharmaceutical requirements apply to combination products.

F. Topics for FDA Guidance

In terms of overall need, the majority of respondents indicated they would like additional guidance on combination product issues. In gauging the need for regulatory guidance on specific topics, the survey offered participants a list of 17 distinct regulatory topics and asked them to select the five topics on which they believe combination product guidance is needed most. Topics included in the list were the following.

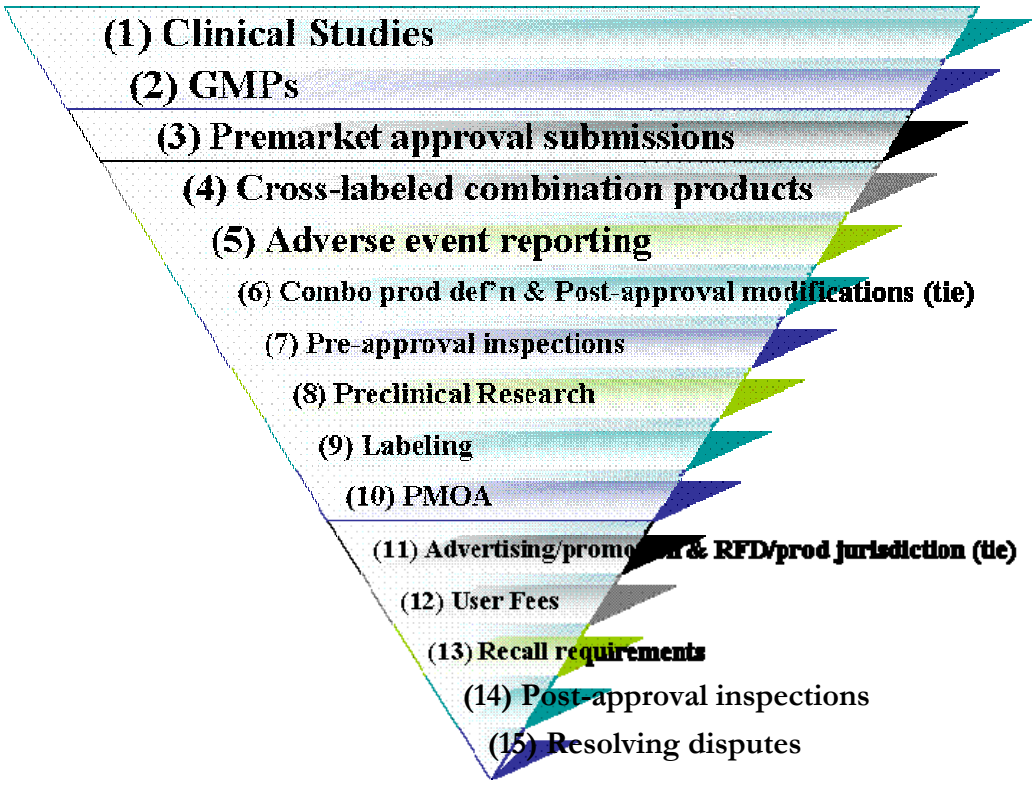
- Adverse event reporting
- Advertising and promotional issues
- Clinical studies
- Combination product definition

- Cross-labeled combination products
- Good manufacturing practices (GMPs)
- Labeling
- Postapproval inspections
- Postapproval modification issues
- Preapproval inspections
- Preclinical research
- Premarket approval submissions
- Primary mode of action
- Recall requirements
- Resolving disputes
- Request for designation (RFD) and product jurisdiction
- User fees

Weighted rankings were determined by assigning selected topics a point value from 1 to 5; a topic ranked first received a point value of 5, a topic ranked second received a value of 4, and so on.

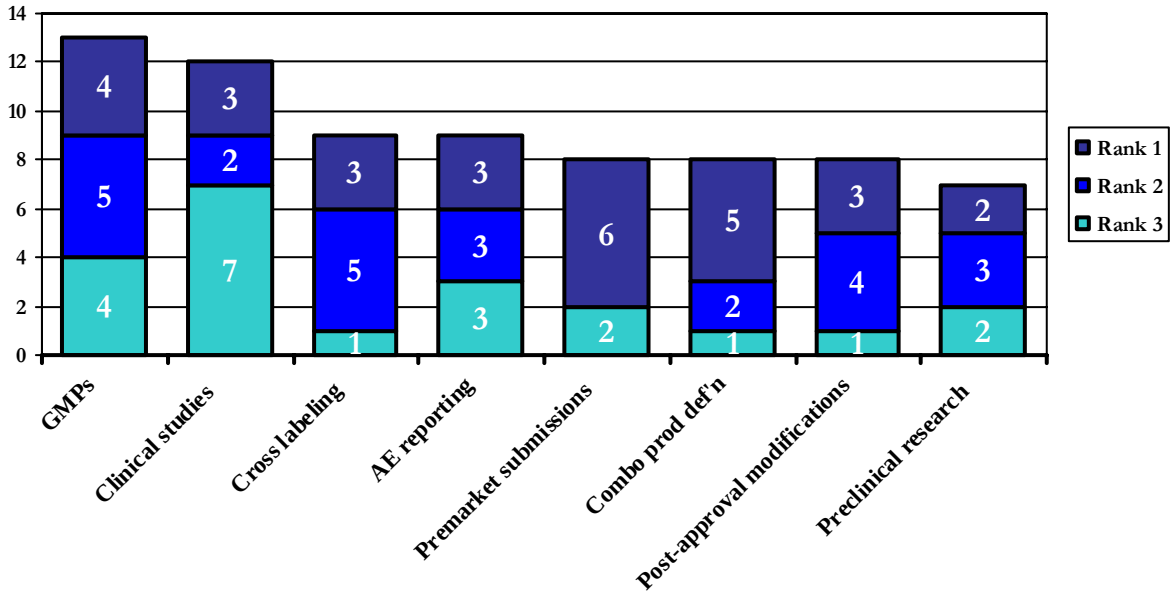
As the figure below shows, when weighted, the number-one topic was clinical studies. GMPs came in second—a subject on a written guidance document does exist and on which the Agency announced its intent to publish a proposed rule in Spring 2006.[2] Premarket approval submissions can in third.

Desired Guidance Topics: Weighted Rankings



When ranked by the raw number of responses, clinical studies and GMPs switched places as the top two topics, with GMPs slightly edging out clinical studies in terms of the number of respondents ranking those subjects in their top three priorities. Cross labeling and adverse event reporting tied for third.

Desired Guidance Topics: Non-Weighted Rankings

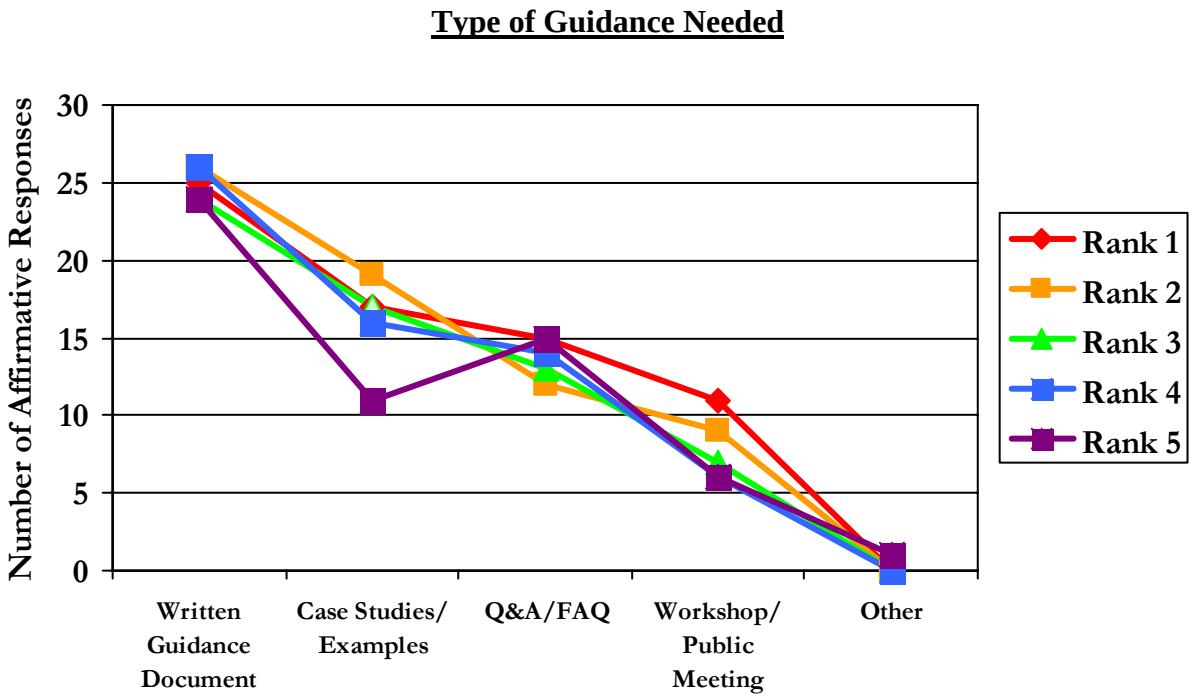


As these figures show, a number of additional topics were cited as being important to many survey participants. These included adverse-event reporting, cross-labeling, postapproval modifications, the definition of a combination product, and premarket submissions.

G. Type and Reason for Guidance

After respondents ranked their priorities for guidance topics, the survey requested additional information about the type of guidance they thought was needed on those topics, and why. Participants could select more than one type of guidance for each subject.

For all ranked guidance topics, the majority of respondents indicated that they would prefer a traditional, written guidance document as a resource. Several respondents also indicated that, in addition to a traditional guidance document, they would like to have either a question-and-answer or frequently asked questions document, documented case studies and examples, or both types of resources. Further, in some cases, respondents would also like FDA to have a public meeting or workshop on a particular topic. However, most respondents preferred guidance in a written format instead of guidance given orally, such as at a meeting.



H. Take-Away Messages

In all, a few key takeaway messages were evident in the results of the CPC survey. First, industry members would like additional guidance—and in more detail—on combination product issues. Second, as informed by both the survey and our discussions with stakeholders, the top priorities on specific topics are as follows:

1. GMPs applicable to combination products
2. Clinical trials on combination products
3. Post-approval product modification issues

Consistent with this message, our organization recently submitted a draft guidance document on clinical research issues pertaining to combination products, and we are planning to co-sponsor a workshop on the GMP proposed rule when it is published. The survey also indicated that stakeholders felt several other topics were important, including premarket submissions, cross labeling, and adverse event reporting.

Last but not least, another equally important aspect of needed policy development is flexibility. As discussed above, combination product technology is evolving at a rapid pace. As a result, nearly any broadly applicable rule or policy may either be almost instantaneously out of date for new combination products, or may simply not make sense for some of them. Because of the unique state of the industry, patients, the Agency, and manufacturers would benefit from early, real-time access to Agency personnel to discuss combination product issues. Enabling such access will foster better, more efficient decision-making that in turn benefits patients and helps to educate and inform the Agency and industry.

VI. CONCLUSION

Today we find ourselves in a time resplendent with opportunities for improving and advancing healthcare through novel combination products. To make the most of these opportunities, we urge the Agency not to lose focus on combination products. The promise for patient care, industry growth, and the complexity and number of issues facing the Agency all argue for increased attention to combination products that enables FDA policy development, continued FDA-industry dialogue, and continuous improvement that keeps pace with this ground-breaking industry.