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THE NEWS THIS ISSUE

- **COMBINATION PRODUCTS ARE FOCUS OF INTENSE ACTIVITY** at FDA, as the Office of Combination Products strives to finalize new regulations and guidances clarifying policies for premarket review and manufacturing quality control. FDA staff promise to take industry concerns into account in final rule concerning "primary mode of action," which will play a crucial role in future assignments of combos to a lead center within the agency. Longstanding questions about the applicability of QS regs and drug cGMPs to combos are answered in a recent draft guidance. For those preparing to enter the combination product world, the stories of firms that have already navigated FDA premarket and compliance channels offer a glimpse of what to expect..... **Below**
- **HOW DID THEY DO IT?** Chart details the route followed by 11 different companies in getting their combination products to market..... **9**

FDA Refines Premarket, GMP Paths For Combination Products

FDA's Office of Combination Products is moving quickly to put in place a system of rules and guidances aimed at giving industry a clearer, more predictable path for the regulation of combination products.

That's good news for companies such as Vyteris, which recently received FDA approval for a novel device-drug product. Delivering medications through the skin via a mild electric current, the ***LidoSite*** iontophoresis system is intended to provide local anesthesia without the use of a needle.

Getting the combo approved and determining which quality control regulations would govern manufacturing was "very challenging," said George Baskinger, Vyteris associate director of regulatory affairs & quality assurance.

With few formal FDA policies to guide them, Baskinger and others at Vyteris did their best to blaze a path to market.

Vyteris submitted two separate applications – an NDA for LidoSite's medicated patch, which was reviewed by FDA's Center for Drug Evaluation & Research, and a 510(k) for the system's electronic dose controller, which was reviewed by the Center for Devices & Radiological Health. CDER served as the lead center for the review.

In developing the product, Vyteris drew on both device and drug design models. The controller was created under the design control requirements of the Quality System Regulation, with close attention paid to risk management and design review procedures.

The patch, meanwhile, was developed according to procedures typically used for drugs, with development reports created for each part of the multi-layered patch, as well as the patch as a whole.

The product's manufacturing process is also governed by two separate regimes. For the controller, which is made by a contract manufacturer, Vyteris follows the QSR. For the patch, which Vyteris produces itself – manufacturing the drug portion in-house and purchasing other components from suppliers – the company follows the pharmaceutical current good manufacturing practices (cGMPs).

This two-pronged regulatory scheme for the manufacturing process was proposed by Vyteris and deemed acceptable by FDA, according to Baskinger. "They said to do what we thought was best," said the Vyteris director.

When manufacturing operations were inspected prior to product approval, FDA sent both a device investigator and a drug investigator. While the drug investigator looked over the patch manufacturing process, the device investigator studied the design history file for the controller.

Vyteris received 510(k) approval for the controller in August 2003, and NDA approval for the patch in May 2004. The components are sold separately, but labeled for use exclusively with each other.

The next problem Vyteris must solve is how to efficiently report adverse events, should they occur. FDA has instructed the firm to send information about any device-related events to CDRH, with a copy to CDER, and any information about drug-related events to CDER, with a copy to CDRH.

That reporting process seems burdensome to Baskinger, who looks forward to seeing FDA's new guidance document on adverse event reporting for combos, due out soon. He says he would prefer a system whereby adverse event reports are all sent to the Office of Combination Products, and coordinated from there.

Baskinger is even more curious to see how future modifications to the controller will be handled. "We'll go to CDRH. But what information will we have to give to CDER? That's the question."

Despite all the pre- and post-market complexities surrounding the LidoSite system, Vyteris – which has seen itself as both a device and a drug firm since its inception as a Becton Dickinson spin-off four years ago – may have had an easier time navigating the dual CDER/CDRH regulatory processes than would a traditional device company.

"For a device company to make a pharmaceutical, and a pharmaceutical company to make a device, it's like two different worlds," Baskinger remarked.

Shepherding a combination product through FDA "takes a lot of skill and a lot of time," said William Clementi, whose firm Clementi & Associates assisted Norwegian manufacturer PhotoCure with the premarket approval process for the ***CureLight BroadBand*** combination product. The product was approved via NDA and PMA in July, with CDER taking the lead and CDRH providing a "substantial" consult, according to Clementi.

Among the challenging tasks when dealing with a combination product, Clementi said, are preparing for meetings with FDA, making sure needed people from all relevant agency units can attend, handling multiple user fee requirements, and communicating with FDA on auditing items for pre-approval inspections.

For instance, Clementi said, "if it's a brand new device and a brand new drug, I think you've got to really work and make [FDA] people understand what the device is all about and how it interacts with the drug" when preparing for the pre-approval inspections.

In the case of CureLight, which received two separate drug and device pre-approval inspections, "we worked very diligently to prepare the device investigator so he could understand when he got there what to look for," said Clementi.

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FDA Finalizing Rule On "Primary Mode Of Action"

All of the issues Vyteris and PhotoCure wrestled with – *e.g.*, how many applications to submit, whether to seek primary regulatory jurisdiction in CDER or CDRH, and which quality control regs to apply to the manufacturing processes – should become easier for combination product firms once FDA finishes work on a series of rules and guidances currently underway.

"The environment is going to change," said Vyteris' Baskinger, who welcomes FDA's efforts to provide a "better defined" process for combination products.

With coordination and leadership from the two-year-old Office of Combination Products, the agency is already well on its way toward providing answers to many questions.

Tackling one of the biggest issues in the combo products arena, FDA in May proposed a regulation for determining which agency center will have primary jurisdiction over individual products.

The PMOA rule clarifies how FDA will handle cases in which the most important therapeutic action of a product cannot be determined.

An agency working group began work in October to finalize the rule. It has vowed to take into consideration numerous comments received from companies and industry associations.

The proposed rule addresses a gap in FDA laws and regulations that has made life difficult for manufacturers and regulators alike. Under Section 503(g) of the FD&C Act, FDA is required to assign a combination product to one agency center (CDER, CDRH, or the Center for Biologics Evaluation & Research) based on the product's "primary mode of action." However, the law does not explain exactly what is meant by primary mode of action.

The regulation, which people are calling the "PMOA rule," will finally establish a formal definition for the term. It also will set forth a method for making assignments in cases where the agency, for one reason or another, is unable to identify a product's primary mode of action.

The proposed reg would define primary mode of action as "the single mode of action of a combination product that provides the most important therapeutic action of the combination product."

In the case of a drug-eluting stent, for example, the primary mode of action is provided by the stent itself, which physically holds open the coronary artery; the drug, meanwhile, plays a secondary role in reducing restenosis and enhancing the stent's effectiveness, FDA explains in the preamble to the proposed rule. Accordingly, the product would be assigned to CDRH for premarket review and regulation, the agency states.

By contrast, in the case of a drug-eluting disc for delivering chemotherapy, the primary mode of action is to prevent tumor recurrence at the implant site, a job performed by the drug; the implantable device component merely offers support by controlling the release of drug. Here, the product would be assigned to CDER, FDA explains.

Sometimes, however, it is not possible to name a product's primary mode of action – a reality FDA acknowledges in the proposed rule. A product may be too early in its development for FDA and the sponsor to fully understand which part provides the most important therapeutic benefit, or the product may have two independent and equally important modes of action. An example of the latter is a contact lens for vision improvement which also provides drug treatment for glaucoma.

In these cases, FDA has proposed using an "assignment algorithm." As a first priority, FDA would assign the product to the center "that regulates other combination products that present similar questions of safety and effectiveness with regard to the combination product as a whole."

In other words, said Office of Combination Products Director Mark Kramer, "we would be assigning this kind of product to a center with direct experience in that type of combination product." Kramer's office is responsible for assigning jurisdiction for combination products.

If there is no center with such experience, FDA would select the center "with the most expertise related to the most significant safety and effectiveness questions presented by the combination product," according to the proposed rule.

This second tier of the algorithm could come into play when a product is the first of its kind, or when it has a different intended use, design or formulation and presents different safety and effectiveness questions

than previous products, Kramer explained. "We'd be assigning it to the center with the most related experience," he said.

Kramer maintains that the approach outlined in the proposed rule is not new. The proposal "is consistent with agency practice, and codifies criteria that the agency has generally used since 1991. But what we've done here is clarified situations where the most important therapeutic action cannot be determined," he said in a May telebriefing.

Kramer and others in the Office of Combination Products say that none of the roughly 300 combination product assignments the agency has made over the last 13 years would have come out differently had the agency used the methodology contained in the proposed rule.

The agency intends to provide more detail about the roles of jurisdictional precedents and the Intercenter Agreements.

The rule will only apply to Requests for Designation submitted by companies after the effective date of the final rule. It will not affect any combination products that already have been assigned to a lead center, OCP staff stress.

Stakeholders Outline Concerns With Agency Proposal

The agency task force working to finalize the PMOA rule is expected to give careful consideration to three key concerns voiced by industry in comments on the proposal.

First, device, diagnostic and biotechnology companies all requested that FDA take into account past jurisdictional determinations – *i.e.*, precedents – when making future decisions about a product's primary mode of action.

Second, several industry commenters urged FDA to confirm that the 1991 "Intercenter Agreements" will remain in effect, even after the final PMOA rule is issued. These agreements – between CDRH and CDER, CDRH and CBER, and CDER and CBER – name specific types of products and identify which center will have premarket approval authority for them. The agreements also discuss the type of marketing applications to be submitted by manufacturers, and whether the lead center must consult with other centers during product review.

Although the 13-year-old intercenter agreements are still in use, it is widely acknowledged, both inside and outside FDA, that they are inadequate in addressing today's more technologically advanced and novel combo products.

Third, industry commenters argued that FDA should consider the intended use of the combination product as a whole when determining primary mode of action.

"We will take into account the comments when we meet to tweak the final rule," Leigh Hayes, product assignment officer/regulatory counsel in the Office of Combination Products, said at the annual meeting of the Regulatory Affairs Professionals Society Oct. 12. "We intend to be more detailed in the preamble about intended use, the role of precedents, and the intercenter agreements," Hayes added.

AdvaMed devoted major attention to these three issues in its August comments on the proposed rule. Urging consideration of precedents, the device trade association noted the "concern and confusion" that could arise for companies "that have relied on prior jurisdictional decisions...to build their product franchises and business." Furthermore, failure to consider precedents may result in "multiple premarket review regimes for similar core technology," AdvaMed said.

AdvaMed suggested that FDA expressly state in the PMOA regulation and its preamble that jurisdictional precedents will inform and guide the agency's decision regarding a product's primary mode of action. In addition, the trade group proposed preamble language emphasizing that the rule is not intended to change previous jurisdictional decisions.

The Biotechnology Industry Organization also stressed the critical role of precedents in product development. Many companies "have embarked on development plans based on precedents established for existing products and which reflect current working relationships with particular centers," BIO commented. These projects could be jeopardized if FDA ignores previous jurisdictional assignments when implementing the rule's algorithm, the group adds.

Abbott, too, recommended "a more definitive statement regarding the role of precedent" in the rule.

The diagnostics company is particularly concerned about how new pharmacogenomic device and drug pairings will be treated if jurisdictional precedents are not taken into account.

Abbott fears that, under the proposed rule, pharmacogenomic diagnostic/drug pairings will be reviewed by CDER or CBER, since the most significant safety and effectiveness questions are related to the drug component. Historically, however, the diagnostic portion of such paired products has been reviewed by the device center – an approach favored by Abbott because of CDRH's "diagnostic expertise."

Abbott thus supports "greater consideration of jurisdictional precedents in informing and guiding decisions on center assignment," the company commented.

For similar reasons, Abbott asked FDA to confirm in the preamble to the final rule that the Intercenter Agreements will remain in effect. The 1991 agreement between CBER and CDRH provides that CDRH will regulate *in vitro* tests or reagents for the detection of infectious agents transmitted by blood, except when the tests are intended only for donor screening.

Medtronic Seeks Separate Guidance For Drug-Delivery Devices, Citing "Unique Issues"

Other stakeholder comments discussed the importance of the Intercenter Agreements as they relate to infusion pumps and other drug-delivery devices. While such products often are regulated as single-entity devices, they sometimes can be considered combination products, depending on how they are configured, marketed and labeled.

Both AdvaMed and Medtronic cited the agreement between CDER and CDRH clarifying that infusion pumps and other drug-delivery devices that are distributed unfilled and do not require a conforming change in drug labeling are devices regulated by CDRH.

Both organizations expressed concern that the proposed PMOA rule, as currently drafted, would redirect regulation of the majority of unfilled delivery systems to CDER or CBER. This could happen because the most important therapeutic action of drug delivery systems comes from the drug or biologic being delivered, not the delivery device itself.

"We do not believe that the agency intended such a result," said Medtronic. "Because delivery systems can be either combination products (subject to the proposed rule) or single-entity devices, clarification is needed regarding the ongoing effect of the Intercenter guidance on this point," the company stated.

In addition, Medtronic urged FDA to issue separate guidance for delivery systems, due to their "unique jurisdictional issues."

Lilly, Too, Prefers CDRH Review Of Delivery Systems

Pharmaceutical company Lilly was primarily concerned about the overly burdensome review that could result if a drug-delivery device were assigned to CDER. "The length of the review would be at least four months and possibly as long as six months because of the CDER performance targets, while a device-only review could be three months," Lilly said.

The company further noted that the drug component of a delivery system poses "no new issues of safety and efficacy...when used in combination with the new device portion."

Elaborating on Lilly's concern, Medtronic stated that the device laws, unlike those for drugs and biologics, require FDA to consider the "least burdensome" requirements in evaluating device safety and effectiveness. As a result, device manufacturers have enjoyed premarket mechanisms available only to products overseen by CDRH, including early collaboration meetings, modular reviews, third-party reviews and humanitarian device exemptions.

It is important "for FDA to acknowledge" that these mechanisms "foster innovation," Medtronic stressed.

It is unclear how FDA will handle the question of drug-delivery devices. "I don't know that we have come to a final decision about those types of products yet, but we are planning to work through in the working group" the example of implantable drug dispensers, Office of Combination Products official Hayes said at the October RAPS meeting.

"We do plan to get back to [industry] with a more detailed answer," she added. "It's under active consideration."

On the third key issue that surfaced in comments on the proposed rule, industry stakeholders want FDA to

confirm that a product's overall intended use will be considered as part of primary-mode-of-action decisions.

Noting that FDA has "for over a decade" considered intended use when making jurisdictional assignments for combos, BIO said intended use should remain "a key determinant in assessing the definition of the therapeutic action of any combination product."

AdvaMed concurred, recommending that the proposed PMOA rule be revised to state that "mode of action is the means by which a product achieves the intended therapeutic function or effect."

Industry Requests More Examples Of PMOA Analysis

In other concerns, industry groups recommended that the rule provide more examples of combination products and how they would be treated.

Current examples in the preamble are "few in number, lack complexity, and are not forward-looking," AdvaMed said. Without examples that anticipate future product innovations, "AdvaMed is concerned that, over time, outdated and unhelpful guidance will be locked into law."

Firms generally will not have to maintain "two separate manufacturing systems" for device-drug combinations, FDA says.

The association suggested that, in addition to adding a more complex case to the preamble, FDA issue a separate guidance document containing examples of several innovative combination products and the agency's jurisdictional decision for each. This way, "the examples can be updated as technology improves, rather than be locked into law," the group noted.

BIO specifically requested examples of combination products that would provide more challenging tests of the rule's assignment algorithm. "In particular, the proposed rule does not provide any examples of drug and biological product [combinations]; device and biological product [combinations]; or drug, device and biological product combinations," the organization observed.

Finally, stakeholders requested clarification regarding the review timeline for combination products. Pharmaceutical Research & Manufacturers of America asked FDA to state in the final rule that review timelines for combination products would be consistent with the performance goals of the primary center.

BIO, meanwhile, suggested that FDA identify "a process for coordinating timelines for combination products that involve multiple submissions."

Guidance Explains QSR/cGMP Applicability To Combos

In addition to wondering which center will review their product, combo developers face the challenge of determining which good manufacturing practice regulations they must meet.

For example, does the manufacturer of a device-drug combination have to comply with the device QSR or pharmaceutical cGMPs, or both? And how will the decision be made?

FDA attempts to provide answers in a new draft guidance, "Current Good Manufacturing Practice for Combination Products." The September document describes a common-sense approach whereby constituent parts of a combination product are subject only to their usual governing regs as long as the parts remain separate. Once the process of joining them into a single entity or packaging them together as a unit begins, both sets of manufacturing regulations apply.

However, FDA reassures industry that it "should generally not be necessary" for combo product firms to maintain "two separate manufacturing systems" in order to comply with both the QSR and cGMPs.

Rather, firms can use the compliance system that is "already operating at a manufacturing facility" and, depending on the product, add on any relevant requirements that are spelled out with greater specificity in the other regulatory scheme.

This is possible, FDA explains, because of the "considerable overlap" between the drug and device manufacturing regs.

For example, a drug firm whose manufacturing controls are set up according to the cGMP requirements in Parts 210-211 of the *Code of Federal Regulations* should "carefully consider" adding the corrective and preventive action provisions of the Quality Systems Regulation (*CFR* Part 820), the guidance notes.

By the same token, a device company operating under the QSR should consider also complying with drug manufacturing requirements concerning expiration dating, stability testing, and testing and release for distribution.

While the good manufacturing practices guidance lays out these general rules of thumb, companies likely will still have questions when it comes to their particular products. The guidance urges manufacturers to discuss their particular situation with the agency.

Firms are encouraged to seek FDA comment on their compliance plans during pre-investigational meetings and throughout development of the combination product. FDA recommends that applicants "include all critical manufacturers in these discussions," and that attention be paid to any "critical steps that may be conducted at source/contract firms and any special testing."

On the agency side, the discussions may include input from reviewers in the lead and consulting product review divisions; compliance experts in the lead and consulting divisions at FDA headquarters and the district office; national expert advisers from the Office of Regulatory Affairs; and staff from the Office of Combination Products.

"FDA will document its recommendations concerning the manufacturer's proposal in FDA meeting minutes, letters, or other permanent communication records, as appropriate. Also, FDA staff should communicate this information to the appropriate District Office," the guidance states.

No comments on the draft guidance have been submitted to date. The comment period ends Dec. 3.

More Than A Dozen Pre-Approval Inspections For A Breakthrough Device-Biologic Combination

Medtronic is among the select group of combo product firms that have succeeded in navigating the cGMP/QSR maze, despite the lack until now of published guidance from FDA.

The company's experience with its ***INFUSE*** Bone Graft/***LT-CAGE*** product shows what a feat it can be to set up manufacturing operations for a complex combination product and – more to the point – to get FDA's nod for the related quality control systems.

The product consists of three main components: a metal spinal fusion cage; a genetically engineered human protein (rhBMP-2) in powder form; and a collagen sponge to carry the protein.

The rhBMP-2 powder and collagen sponge are packaged together in a kit that also contains sterile water (used to mix the protein powder into a liquid solution) and a syringe. The metal cage device is packaged and sold separately.

The combination product was approved via PMA in 2002 for the treatment of degenerative disc disease in the lower spine. Surgeons soak the sponge with the rhBMP-2 solution and place it inside the cage; the cage is then implanted between the patient's vertebrae, where the rhBMP-2 promotes new bone growth to fuse the spine.

CDRH was the lead center in reviewing the product, with CBER and CDER providing consults, according to Rick Treharne, senior VP, regulatory affairs, at Medtronic Sofamor Danek.

Seemingly every existing manufacturing quality control requirement comes into play in the making of the product. The metal cage is manufactured by Medtronic Sofamor Danek in accordance with the QSR. The collagen sponge is manufactured for Medtronic by a vendor, Integra, also under the QSR.

The rhBMP-2 protein, meanwhile, is manufactured for Medtronic by Wyeth BioPharma in accordance with the biologics regulations. And the sterile water is produced by a supplier in compliance with the pharmaceutical cGMPs.

Not the least of Medtronic's challenges was managing FDA's pre-approval inspections, of which there were a whopping 14. The process was "harder than normal," said Treharne.

FDA sent device, biologics and drug investigators to examine clinical study sites, vendor manufacturing plants and Medtronic facilities.

In addition, since product approval, four routine inspections of manufacturing sites have been conducted.

In April, CDRH approved a second indication for the INFUSE Bone Graft product. In what Susan Alpert, Medtronic VP, chief quality & regulatory officer,

termed a "proof of concept" advance, the rhBMP-2 protein and collagen sponge can now be used to treat acute, open fractures of the leg's tibia bone.

Dispute Resolution, User Fee Draft Guidances Provide Further Direction For Manufacturers

In addition to the GMP document, the Office of Combination Products also this year released draft guidances on dispute resolution and user fees.

The dispute resolution draft, issued May 4, explains how companies should go about requesting help from OCP when they believe that FDA has been too slow in reviewing and acting upon a premarket application for a combination product.

Two user fees for a combination product could represent a significant barrier to innovation, draft guidance acknowledges.

The draft guidance recommends that sponsors and applicants first "try to resolve issues and disputes with the lead division, office and center." If problems remain, sponsors are advised to contact the Office of Combination Products, which will work with the various parties to facilitate prompt completion of the review.

In evaluating dispute resolution requests, the office will consider the premarket review performance goals set under MDUFMA and the Prescription Drug User Fee Act (PDUFA). The draft guidance notes OCP's belief that the goals apply to combination products in the same way they do to non-combination products.

"When a combination product is to be reviewed under one premarket application, OCP believes that the performance goals associated with that type of premarket application would apply," the guidance notes. When a combination product is reviewed under two premarket applications, "FDA believes that the performance goals associated with both types of premarket applications would apply."

OCP suggests that sponsors wait until after applicable performance goal timelines have passed before submitting a dispute resolution request. However, if a sponsor receives advance notice that a center will not meet a review deadline, an earlier request would be acceptable, as it would "further the goal of obtaining review as quickly as possible," the guidance explains.

A September draft guidance explains how user fees will be determined for combination products. It states that combination products for which a single marketing application is submitted will be assessed the user fee associated with that particular type of marketing application. When FDA requires two marketing applications for a combo – an "infrequent" situation, the document notes – two application fees would ordinarily be assessed.

If a sponsor voluntarily submits two applications when only one is necessary, FDA still would assess two fees. The draft notes that firms may perceive a benefit in submitting two applications when they are seeking new drug product exclusivity, orphan status, or proprietary data protection when two firms are involved.

Nevertheless, "review of two applications when one would suffice places extra burden on FDA review resources, and a user fee for each application would ordinarily be assessed," the draft guidance states.

The document explains that sponsors may be eligible for existing waivers or fee reductions under MDUFMA or PDUFA. In particular, the agency "intends to look closely at whether a PDUFA 'barrier to innovation' waiver may be appropriate to reduce the additional fee burden associated with FDA's requirement for two marketing applications," the draft notes.

"FDA believes that the assessment of two marketing application fees for an innovative combination product could represent a significant barrier to its development," the agency explains.

The draft guidance describes the characteristics of "innovative" products and spells out how FDA will decide whether a particular innovative combination product is eligible for a fee reduction.

If FDA requires two applications for an innovative combination product, the agency "would expect to reduce the PDUFA fee by the amount of the MDUFMA fee," the guidance states. "Thus, a sponsor would pay the full MDUFMA fee associated with the type of MDUFMA application, and a PDUFA fee reduced by the paid MDUFMA fee. The total amount paid would be equivalent to one PDUFA fee."

Fiscal 2005 user fees are $239,237 for a PMA ($90,910 for small businesses) and $3,502 for a 510(k) ($2,802 for small businesses). The FY 2005 fee for a new drug application is $672,000.

Comments on the user fee draft guidance are due Nov. 29.

Coming Next: More Guidances, More Postmarket Attention, And An Evaluation Of How It's All Working

OCP staff report that additional draft guidances will be released soon advising industry how to report adverse events for combination products, and how to determine the appropriate number of premarket applications for a combination product.

The office also is thinking about whether premarket submissions for combination products should have their own specific format and content requirements. "We are considering whether or not this would be a worthwhile approach," said the office's Leigh Hayes.

Finally, OCP plans to hold a public meeting in the first half of 2005 to obtain input on cross-labeling issues for combination products.

"It's a very sticky, complex regulatory issue" that concerns "when, for example, a drug might need to be relabeled in order to reflect its use with a device," OCP Director Kramer explained at a Nov. 18 MDUFMA stakeholder meeting in Gaithersburg, Md.

Kramer added that his office "has some ideas that we think will help finally solve" the matter. Next year's meeting, which has yet to be scheduled, is intended "to get more public comment on this whole issue, with an eye toward rulemaking," he said.

Kramer has made it clear he won't be satisfied until his office has finished the job of establishing a clearer approach for the jurisdictional assignment, premarket review and postmarket regulation of combination products.

"I think we have a lot of work left to do," he said at the Nov. 18 MDUFMA meeting. "Everything we've done so far is in draft." Topmost goals, he indicated, are to finalize the primary-mode-of-action rule and existing draft guidances.

Looking ahead, Kramer anticipates the office turning its attention to "downstream" issues such as post-approval changes to products and promotion and advertising matters. These and other postmarket issues "were not among our initial priorities, but really, within the whole regulatory framework, they need to be thought through," he said.

Finally, the office plans to analyze the impact of its many activities. "I think that will take some time, to just sit back and monitor whether in fact these things are making a difference," said Kramer. "I don't think we are there [yet], but we will need to have that evaluation." ♦♦

Combo Product Approvals: Differing Strategies For Success

The following chart provides examples of various regulatory pathways for combination products. Each entry specifies the product name, manufacturer, components, combination type, indication, application(s), lead FDA center and filing/approval dates. The list is not intended to be comprehensive, but rather to offer a perspective on the range of approaches pursued by companies.

INFUSE Bone Graft	
Manufacturer:	Medtronic Sofamor Danek
Components:	Recombinant human bone morphogenetic protein (rhBMP-2); absorbable collagen sponge; sterile water
Type of combination:	Components packaged together in a kit
Indication:	For use in the treatment of acute, open tibial shaft fractures that have been stabilized with IM nail fixation
Application:	PMA
Filed:	December 20, 2000
Approved:	April 30, 2004

Lead center:	CDRH
Notes:	1) The PMA was originally submitted to FDA by Wyeth and transferred to Medtronic immediately following FDA approval for this indication. 2) As a result of FDA's June 2003 decision to transfer regulatory responsibility for some therapeutic biological products from CBER to CDER, the center for drugs would now provide the consulting review for the bone morphogenetic protein component of this combination product.
INFUSE Bone Graft/LT-CAGE Lumbar Tapered Fusion Device	
Manufacturer:	Medtronic Sofamor Danek
Components:	LT-CAGE metallic tapered spinal fusion cage; INFUSE Bone Graft (rhBMP-2, absorbable collagen sponge, sterile water)
Type of combination:	INFUSE Bone Graft components packaged together in a kit; LT-CAGE packaged and sold separately
Indication:	For treatment of degenerative disc disease (DDD) in the lower back
Application:	PMA
Filed:	(not available)
Approved:	July 2, 2002
Lead center:	CDRH
Note:	As a result of FDA's June 2003 decision to transfer regulatory responsibility for some therapeutic biological products from CBER to CDER, the center for drugs would now provide the consulting review for the bone morphogenetic protein component of this combination product.
OP-1 Putty	
Manufacturer:	Stryker Biotech
Components:	Recombinant human Osteogenic Protein 1 (bone morphogenetic protein); Type I Bovine Bone Collagen Matrix; thickening agent
Type of combination:	Components packaged together (one vial of OP-1 and bovine collagen, one vial of thickening agent). Components are combined with sterile saline to produce the product.
Indication:	For use as an alternative to autograft in compromised patients requiring revision posterolateral (intertransverse) lumbar spinal fusion, for whom autologous bone and bone marrow harvest are not feasible or are not expected to promote fusion
Application:	Humanitarian device exemption (HDE)
Filed:	August 18, 2003
Approved:	April 7, 2004
Lead center:	CDRH
CureLight BroadBand	
Manufacturer:	PhotoCure ASA
Components:	CureLight BroadBand (Model CureLight 01) photodynamic therapy light; methyl aminolevulinate HCl cream
Type of combination:	Components packaged separately but labeled for use as a system

Indication:	For treatment of non-hyperkeratotic actinic keratoses of the face and scalp in immunocompetent patients when used in conjunction with lesion preparation when other therapies are unacceptable or considered medically less appropriate
Application:	Separate applications submitted to CDRH and CDER: PMA (CureLight BroadBand), NDA (methyl aminolevulinate cream)
PMA filed:	September 27, 2001
PMA approved:	July 28, 2004
NDA received:	September 26, 2001
NDA approved:	July 27, 2004
Lead center:	CDER
LidoSite Topical System	
Manufacturer:	Vyteris
Components:	LidoSite Patch (lidocaine HCl/epinephrine topical iontophoretic patch); LidoSite Controller iontophoresis device
Type of combination:	Components packaged separately but labeled for use exclusively with each other
Indication:	For use as a topical local anesthetic delivery system indicated for use on normal intact skin to provide local analgesia for superficial dermatological procedures such as venipuncture, intravenous cannulation, and laser ablation of superficial skin lesions, on patients 5 years of age and older
Application:	Separate applications submitted to CDRH and CDER: 510(k) (controller), NDA (patch)
510(k) received at FDA:	May 19, 2003
510(k) approved:	August 20, 2003
NDA received at FDA:	September 25, 2002
NDA approved:	May 6, 2004
Lead center:	CDER
CYPHER Sirolimus-Eluting Coronary Stent	
Manufacturer:	J&J/Cordis
Components:	Stent; sirolimus
Type of combination:	Components are produced as a single entity
Indication:	For improving coronary luminal diameter in patients with symptomatic ischemic disease due to discrete *de novo* lesions
Application:	PMA
Filed:	June 28, 2002
Approved:	April 24, 2003
Lead center:	CDRH
FluMist Influenza Virus Vaccine	
Manufacturer:	MedImmune Vaccines
Components:	Nasal spray system (glass syringe barrel and Teflon sprayer nozzle); biologic product (influenza virus vaccine, live, intranasal)

Type of combination:	Packaged and distributed as prefilled unit.
Indication:	For active immunization for the prevention of disease caused by influenza A and B viruses in healthy children and adolescents, 5-17 years of age, and healthy adults, 18-49 years of age
Application:	BLA
Filed:	(not available)
Approved:	June 17, 2003
Lead center:	CBER
Photodynamic Therapy with PHOTOFRIN	
Manufacturer:	Axcan Scandipharm
Components:	Wizard X-Cell Photodynamic Therapy Balloon with Fiber Optic Diffuser; PHOTOFRIN (porfimer sodium) for injection
Type of combination:	Components packaged separately but labeled for use exclusively with each other
Indication:	For ablation of high-grade dysplasia in Barrett's esophagus patients who do not undergo esophagectomy
Application:	Separate applications submitted to CDRH and CDER: PMA (Wizard X-Cell); NDA (PHOTOFRIN)
PMA filed:	May 31, 2002
PMA approved:	August 1, 2003
NDA received:	May 31, 2002
NDA approved:	August 1, 2003
Lead center:	CDER
Dermagraft	
Manufacturer:	Smith & Nephew Wound Management
Components:	Dissolvable mesh material; cryopreserved human fibroblast-derived dermal substitute
Type of combination:	Components produced as a single entity
Indication:	For use in the treatment of wounds associated with Dystrophic Epidermolysis Bullosa
Submission:	HDE
Filed:	July 16, 2002
Approved:	July 7, 2003
Lead center:	CDRH
Simplex P Bone Cement with Tobramycin	
Manufacturer:	Stryker Howmedica Osteonics
Components:	Liquid monomer; powder copolymer containing Tobramycin antibiotic
Type of combination:	Cement is packaged in two sterile components
Indication:	For the fixation of prostheses to living bone for use in second stage of a two-stage revision for total joint arthroplasty
Submission:	510(k)

Received:	February 4, 2003
Approved:	May 6, 2003
Lead center:	CDRH
Pegasys (Peginterferon alfa-2a) for combination therapy with Copegus (Ribavirin, USP)	
Manufacturer:	Hoffmann-La Roche, Inc.
Components:	Peginterferon alfa-2a; Ribavirin, USP
Type of combination:	Components packaged separately but labeled for use with each other
Indication:	For the treatment of adults with chronic hepatitis C virus infection who have compensated liver disease and have not been previously treated with interferon alpha
Applications:	Separate applications submitted to CBER and CDER: BLA supplement (Pegasys); NDA (Copegus)
BLA supplement approved:	December 3, 2002
NDA received:	June 3, 2002
NDA approved:	December 3, 2002
Lead center:	CBER
Note:	As a result of FDA's June 2003 decision to transfer regulatory responsibility for some therapeutic biological products from CBER to CDER, the center for drugs would now be the lead center and would review both components of this combination product.
Dermal Collagen Implants (CosmoDerm 1 Human-Based Collagen, CosmoDerm 2 Human-Based Collagen, CosmoPlast Human-Based Collagen)	
Manufacturer:	Inamed
Components:	Highly purified human-based collagen dispersed in phosphate-buffered physiological saline containing 0.3% lidocaine
Type of combination:	Components are packaged as a single entity
Indication:	For injection into the superficial papillary dermis for correction of soft tissue contour deficiencies, such as wrinkles and acne scars (CosmoDerm 1 and CosmoDerm 2); for injection into the mid to deep dermis for correction of soft tissue contour deficiencies, such as wrinkles and acne scars (CosmoPlast)
Application:	PMA supplement
Filed:	May 16, 2001
Approved:	March 11, 2003
Lead center:	CDRH