November 29, 2004

Division of Dockets Management
5630 Fishers Lane
Rm. 1061
Rockville, MD 20852

Re: Docket No. 2004 D-0410

Dear Sir/Madam:

This comment is filed on behalf of the Cook Group, Inc. ("Cook"), a holding company of international corporations engaged in the manufacture of diagnostic and interventional products for radiology, cardiology, urology, gynecology, gastroenterology, wound care, emergency medicine, and surgery. Cook pioneered the development of products used in the Seldinger technique of angiography, and in techniques for interventional radiology and cardiology. Cook products benefit patients by providing doctors with a means of diagnosis and intervention using minimally invasive techniques, as well as by providing innovative products for surgical applications. Cook sells over 15,000 different products which can be purchased in over 60,000 combinations. Many of these devices are used by physicians in the care and treatment of children.

INTRODUCTION

The Cook Group appreciates the opportunity to submit comments to the above-referenced docket in response to the United States Food and Drug Administration's (FDA's) draft *Guidance for Industry and FDA Staff: Application User Fees for Combination Products* (September 2004). Below we identify points of agreement and dispute, and make recommendations in instances where we believe change in the draft guidance is necessary under the law or will facilitate its purpose of clarifying the applicability of user fees to combination products, in particular, to combination device products.

COMMENTS

In general, we agree with the guidance's approach to assessing user fees for combination products. However, we believe a prefatory comment regarding determination of combination product jurisdictional identity is important because of the great disparity between user fees for drugs and devices.

The assessment of user fees is grounded in the jurisdictional identity of products. Therefore, a combination product's jurisdictional identity as a drug, biologic, or device is directly and substantially related to the cost of FDA user fees. Drug products and biologics subject to drug user fees are subject to application, establishment, and product fees. Devices and biologics that meet the definition of a device are subject to application user fees only. Drug product ($41,970) and especially establishment ($262,200), fees are significant and similar fees were not enacted for devices in the Medical Device User Fee and Modernization Act (MDUFMA). *See* H.R. Rep. 107-728, at 27 (2002) ("Unlike the fees assessed under the Prescription Drug User Fee Act (PDUFA), no annual fees are charged for [device] establishments and products."). In addition, drug application user fees are significantly higher than device user fees ($672,000 for a full NDA with clinical data versus $239,237 for a full PMA with clinical data, or $90,910 for a small business's full PMA with clinical data).

There was a reason for the difference in approach and fee amounts in MDUFMA from PDUFA. Device firms are typically smaller than pharmaceutical companies. *See id.* at 27 (device companies typically have less than 50 employees). In addition, the average life cycle for a new medical device is less than one year compared with multi-year cycles for other FDA-regulated products. *See id.* at 21. Because of the small and innovative nature of device companies, it is critical that jurisdictional identity be correctly determined when devices are combined with drugs or biologics. As we have discussed in our previous comments on combination product issues (and therefore will not repeat at length here),[1] section 503(g) of the Act was not intended to create broad discretion in selecting agency Centers to regulate products that include a combination of regulated articles; to the contrary, it was intended to create "firm ground rules" to eliminate discretion and require combination product placements based on primary mode of action. Simply put, the intent was that if a combination product met the definition of a device, it should be regulated as one. If it did not, it should be regulated as a drug or biologic.

Indeed, there is no question that the meaning of "primary mode of action" in section 503(g) of the Act bears a direct relationship to the limitation in the device definition that a device "does not achieve its primary intended purposes through [chemical or metabolic action within or on the body of man or other animals]", § 201(h) of the Act. In 1990 when Congress enacted section 503(g), it amended section 201(h) at the same time to substitute "its primary intended

[1] *See* August 20, 2004 comment to docket No. 2004N-0194 (primary mode of action definition); January 24, 2003 comment to docket No. 2002N-0445 (public hearing on combination product issues); and August 23, 2002 comment to docket No. 2002N-0169 (combination products containing live cellular components).

purposes" for the former language "any of its principal intended purposes"). In other words, the determination of a combination product's identity as a device or drug, in the context of its "primary intended purpose[]", i.e., the intended use of the combination as a whole, is determinative of the primary mode of action of the combination product. Accordingly, Congress intended that combination products would be jurisdictionally classified as a device, drug, or biological product,[2] unless in rare instances a combination product had no primary mode of action, necessitating two or more jurisdictional designations and market clearances as a result, *see, e.g.,* S. Rep. No. 101-513, at 31 (1990) (discussing how the maker of a novel drug delivery system would be required to obtain two market clearances, one for the drug and one for the device). This approach maintained consistency with the structure of the FD&C Act because the Act's approval and enforcement authorities relate exclusively to drugs and devices, not combination products.

For the same reasons and just like a single entity product, a combination product's jurisdictional identity as a drug, device or biologic is determinative of the user fees applicable to the product. Specifically with regard to combinations including device constituents, if the combination does not principally achieve its primary intended purpose by chemical or metabolic action in or on the body of man, it meets the definition of a device under section 201(h) and must be regulated as such by CDRH, including the application of device user fees to the product, to the extent they are required.

While we agree that a device firm manufacturing a combination product that is jurisdictionally a drug or biologic is subject to drug or biologic product approval authority, the potential imposition of drug user fees on most device manufacturers, particularly the ongoing product and establishment fees that are not part of the medical device user fee structure, would likely inhibit them from developing and manufacturing a combination device/drug or device/biologic that would be subject to PDUFA fees. In sum, these fees would represent a significant barrier to innovation for most device firms. Thus, without special consideration of this situation, because most device firms are significantly smaller and less financially supported than pharmaceutical companies, the public health will be adversely affected, even when only one application and application fee are required for a combination drug/device that is regulated as a drug. This result clearly conflicts with the intention of the guidance, which is to avoid barriers to innovation.

Although the PDUFA waiver of the first NDA or BLA fee for a small business is helpful, should a device firm wish to further innovate and file a supplement to its approved NDA or BLA, hefty supplement application fees could apply. In addition, it does not appear that there is much potential for obtaining relief from subsequent application fees or from establishment or

[2] Under the FD&C Act and for purposes of primary mode of action analysis, biologics are considered drugs. Drugs with a chemical or metabolic mode of action that is a result of a biologic or analogous constituent, as defined in the PHS Act and the biologics regulations, are regulated as biologics. Whether CDER or CBER would have responsibility for regulating a combination determined to be a biologic would be based upon FDA's administrative product assignment rules for biologics. Biologics that meet the definition of a device, typically those with a structural mode of action or that are the active ingredient in an in vitro diagnostic unrelated to screening the blood supply, are regulated as devices. The definition of device in section 201(h) is the principal key to the jurisdictional distinctions between devices, drugs, and biologics, whether single entity or combination products.

product fees under the barrier to innovation section of PDUFA. First of all, FDA's 1993 draft guidance on evaluating waivers or reductions based on barrier to innovation or public health, *Interim Guidance Document for Waivers and Reduction in User Fees* (July 16, 1993)(1993 Guidance), is outdated and should be redrafted to reflect current MDUFMA and combination product considerations, as well as to be more useful in understanding the likelihood of a waiver of an application, establishment, or product fee (aside from the current full waiver for the first NDA submitted by a small business).

Secondly, as currently drafted, the 1993 Guidance states FDA is likely to evaluate fee waiver or reduction requests based on the annual revenues of a business and its affiliates and will unlikely grant waivers or reductions to companies with revenues of $10 million or greater. In other words, companies with revenues of less than ten million dollars are more likely candidates for reductions or waivers and will be evaluated on a case by case basis. The 1993 Guidance is thus inconsistent with the device user fee provisions of MDUFMA and thereby rules out barrier to innovation or public health waivers or reductions for many device companies that are considered small businesses for purposes of reduced device fees. Such companies may generate revenues of up to 30 million dollars under MDUFMA and remain eligible for small business allowances, but under the 1993 draft guidance those with revenues of between $10 million and $30 million would not get a break on PDUFA fees. This result ignores the different policy underpinning drug and device user fees.[3] Certainly, it undermines Congressional intent regarding lessening burdensome user fees on small and innovative device companies. In light of the significant burden, and thus barrier to innovation, imposed by PDUFA fees on combination drug/device products manufactured by device companies, FDA should revisit its 1993 Guidance and the criteria by which it judges fee burdens on innovation and the public health.

Because the 1993 Guidance's approach would undermine MDUFMA's recognition of the need for protection of the innovative nature and frailty of medical device firms, we believe that drug establishment and product fees should be presumptively waived for a device firm that begins manufacturing a combination product containing device and drug constituents that is regulated as a drug, if the drug constituent is not made by the device firm. In this instance, requiring establishment and product fees would unnecessarily tax a device firm with no drug product and no drug manufacturing capability in a manner exceeding the fee responsibilities that Congress intended for device firms. This is particularly true where a drug used in a combination is already marketed and an establishment and product fee are paid by the drug manufacturer; such double billing would unfairly burden the device company and provide a windfall to the agency.

Most device firms simply cannot afford the additional fees; this point is reflected by Congress's determination that a drug establishment fee alone, which as stated above is $262,200 for FY 2005, can exceed the FY 2005 device application user fee of $239,237 for a full PMA with clinical data. Further, small device businesses are subject to even lower device application

[3] Moreover, the guidance states that even small start-up companies would not likely qualify for reductions or waivers, because they will likely qualify for the small business first NDA fee and will not before have paid product or establishment fees.

fees (i.e., $90,910 for a full PMA with clinical data). Like "small business" drug companies and their affiliates (less than 500 employees), which get their first NDA fees waived, "small business" device companies and their affiliates (less than 30 million dollars in gross revenues or sales) get their first PMA fee waived. In addition, however, small device businesses receive a continuing significant break (from 25% to 44% depending on the type of application) on device application fees. *See* H.R. 107-728, at 27 (stating that the Committee "understands that the device industry is very different from the drug and biologic industries" and setting out the percentages of each full fee small businesses pay*); see also Important Information on the Medical Device User Fee Rates for FY 2005* (setting out standard and small business fees).[4] As a result, receiving relief from additional drug fees is necessary to maintain Congress's intent of protecting innovation in the device industry. Imposing much higher and additional PDUFA fees on device small businesses creates a barrier to innovation for most of them, thus adversely affecting the public health.

Finally, while we support the proposal to reduce user fees when two applications would be required, reduction of drug fees should be considered even when only one application and fee is involved for an innovative combination product. The public health is affected no matter how many fees are involved when the drug fee presents a barrier to innovation. Additionally, when two fees are involved for an innovative drug/device combination, there is nothing magical about the device fee that makes it the measure of the reduction of the overall fee, and such a reduction is not nearly enough to remove the fee barrier to innovation—a resulting full PDUFA fee is still over seven times the cost of a full PMA fee for a small business under MDUFMA. We recommend reducing the PDUFA fee by the amount necessary to obtain a result in which the applicant is paying no more than 50% of the total combined fees, and reducing the PDUFA fee by more when necessary to protect the device firm as Congress intended.[5]

CONCLUSION

We appreciate the opportunity to file these comments with the agency. Cook Group, Inc., hopes FDA will carefully consider the Act's jurisdictional requirements when making combination product designations. Further, the agency should revisit its criteria for granting PDUFA waivers and reductions for fees creating a barrier to innovation and/or an adverse effect

[4] http://www.fda.gov/cdrh/mdufma/fy2005summary.pdf

[5] This result would equitably recognize the differences between large and small businesses as well as the fact that two reviews would be occurring. For example, for a small device company that makes a combination drug/PMA device, the total combined fees would be $90,910 + $672,000 = $762,910, and one-half would equal $381,455. In this scenario, $381,455 would be taken out of the PDUFA fee; however, the PDUFA fee would still be $290,545, over three times that of the MDUFMA fee; indeed, the agency here should consider using its discretion to make even a larger reduction in the PDUFA fee. For a standard device company, the total combined fees would be $911,237 ($672,000+ $239,237), thus one-half would be $455,618.50. To obtain that result, the PDUFA fee would be lowered from $672,000 to $216,381.50.

on the public health, and consider significant reductions in drug fees for device/drug combinations whether two applications or one are involved.

Sincerely,

Stephen L. Ferguson

Stephen L. Ferguson
Executive Vice President and
Chairman of the Board,
Cook Group, Incorporated