



December 3, 2004

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

Re: Docket No. 2004D-0431

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, Current Good Manufacturing Practice for Combination Products* (September 2004). Below we provide general comments on the approach of the guidance overall, and then provide specific comments on its content. Our general and specific comments identify points of agreement and dispute, and make recommendations in instances where we believe change in the draft guidance is necessary under the law or will facilitate its purpose of

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clarifying the applicability of current good manufacturing practices (cGMPs)¹ to combination products.

Additionally, in our general comments, we point out that an underlying agency assumption in the guidance appears to be that a combination product designation has jurisdictional significance, thus permitting the applicability of cGMPs to combination product constituent parts and finished products independent of the legal status of the constituents, *i.e.*, as component or finished product, or the legal status of combination product a whole, *i.e.*, as a device, drug or biological product. If a combination product is made up of constituents that are themselves a drug product or finished device, we agree that each constituent must comply with the cGMPs required for products with its jurisdictional identity as a drug or device. However, where each constituent part is only a component of a combination product regulated as a drug or device, we do not agree that cGMPs apply to such components. Indeed, FDA's drug cGMP regulations do not apply to constituent parts that are not drug products, *i.e.*, finished dosage forms,² and the QSR does not apply to constituent parts, *i.e.*, components, that are not finished devices.³ Moreover, it is the jurisdictional identity of a combination product as a whole that in the first instance determines which cGMPs apply to the combination. For example, if a drug/device combination product is as a whole a device, it is the QSR, not drug cGMP, that applies. Measures implemented under QSR requirements such as design controls, purchasing controls, and acceptance activities will ensure the product is safe and effective. Additionally, the QSR is sufficiently general that it could accommodate drug or biologic components. Nonetheless, the Act would not require that the GMP measures taken under the QSR for drug or biological components are necessarily the same as those that would be required under drug cGMPs or the biologics regulations. Importantly, those drug cGMP standards would not be enforceable against the finished combination device product.

GENERAL COMMENTS

Legal Background

In 1990, Congress identified the reason for creating section 503(g) of the Federal Food, Drug, and Cosmetic Act (the "FD&C Act" or the "Act") to regulate the designation of combination products by stating, "[t]his provision will provide the Secretary with firm ground rules to direct products promptly to that part of the FDA responsible for reviewing articles that provide the primary mode of action of the combination product." S. Rep. No. 101-953, at 30

¹As used herein, cGMPs will refer to (and be used interchangeably with) cGMPs for drugs in 21 CFR Parts 210 and 211, the Quality System Regulation (QSR) for devices in 21 CFR part 820, the additional GMP, establishment, and product standards for biological products regulated under section 351 of the Public Health Service (PHS) Act in 21 CFR Parts 600-680, the standards for tissue processing in Part 1270 (until they are revoked), and the current good tissue practice rules under Part 1271 (GTPs) for human cells and tissues or cellular or tissue-based products (HCT/Ps) regulated under section 361 of the PHS Act.

² See 21 CFR § 211.1 (drug CGMPs apply to "drug products" and § 210.3(b)(4) (defining "drug product" as a finished dosage form). While the Act's cGMP adulteration provision does not distinguish between finished and unfinished dosage forms, FDA has not promulgated cGMPs for bulk pharmaceuticals.

³ See 21 CFR § 820.1(a) (stating that the QSR applies to "finished devices") and § 820.3 (defining "component" and "finished device").

(1990). Accordingly, new section 503(g) straightforwardly required that after the agency determined the “primary mode of action of the combination product”, “the persons charged with the premarket review [of the component providing the primary mode of action of such a product would] have primary jurisdiction.” *See* former § 503(g)(1) (West 1999). This approach was not intended to create broad discretion in selecting agency Centers or standards 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.

The Medical Device User Fee and Modernization Act of 2002 continued Congress’s efforts to provide clear rules for combination product regulation, and placed a particular emphasis on regularizing postmarket requirements. Specifically, Congress required that the newly created Office of Combination Products ensure “consistent and appropriate postmarket regulation of like products subject to the same statutory requirements to the extent permitted by law.” *See* § 503(g)(4)(A) of the Act; *see also* § 503(g)(4)(D).

As we explained in our previously submitted comments on FDA’s proposed rule defining primary mode of action,⁴ there is no question that the meaning of “primary mode of action” in section 503(g) 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 (which Congress amended at the same time to substitute “its primary intended 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,⁵ 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.

⁴ *See* August 20, 2004 comment to docket No. 2004N-0194. *See also* November 29, 2004 comment to docket No. 2004 D-0410 (combination product user fees); 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).

⁵ 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.

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 cGMPs 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, it meets the definition of a device under section 201(h) and must be regulated as such by CDRH, including the application of the QSR to the product's manufacturing.

The specific authority for enforcing cGMPs for drugs and devices underlines the point. That authority stems from the adulteration provisions of the Act that apply to drugs and devices in section 501 and the prohibited acts that apply to drugs and devices in section 301.⁶ There is no adulteration provision or prohibited act for a combination product. Indeed, combination products have no independent jurisdictional significance of any sort under the Act. Unless a constituent part is an independent finished product, or its cGMPs coincide with that of the product as a whole, that constituent part's cGMPs do not apply. The cGMPs applicable to the jurisdictional identity of the combination apply to the product as a whole and are the only cGMPs that can be enforced under the law.

The Legally Incorrect Approach of the Guidance

Instead of relying on the jurisdictional identity of the combination product as a whole to determine which cGMPs apply, the guidance incorrectly takes the approach that the constituent parts determine the applicable cGMPs. That approach is legally incorrect, unless the constituent parts have independent jurisdictional identities as finished products. For example, a marketed finished dosage form of a drug and a cleared or approved drug delivery system that are proposed for use together may require one, two, or no market clearances depending on their current labeling. Whatever the path to market for the combination, the constituents would remain subject to the drug cGMPs and the QSR respectively, whether they are copackaged or sold separately for use in combination. However, for products with constituent parts that have no independent jurisdictional identity as finished products, whether combined or copackaged, only the cGMPs applicable to the finished product would apply. For example, under agency precedent a drug coated stent is regulated as a device; therefore, the QSR should apply. QSR design controls and purchasing and acceptance activities should principally govern the specifications for the coating and QSR processing controls would govern its application to the stent. Drug cGMPs are guidance regarding the kinds of specifications the drug coating should meet and the type of controls that are reliable in meeting them. However, alternative methods should also be acceptable to the agency under the QSR as long as the coated stent meets its specifications, including that the stent and coating possesses their purported strength, purity, and quality.

A principal concern we have with the guidance is that it does not interpret current cGMP or QSR requirements or provide guidance on the appropriateness of their application to

⁶ Biologics are typically subject to the drug adulteration provisions and derivative regulations under the Act. Where they meet the definition of a device, they are subject to device adulteration authority.

combination products regulated as drugs or devices; instead it attempts to expand without authority the reach of specific requirements, *i.e.*, engraft specific drug cGMP requirements onto the QSR and vice versa. While guidance is helpful in addressing combination product quality issues, notice and comment rulemaking is necessary for enforcement of the suggested quality approaches. Below in our specific comments (discussing section III.A of the guidance) we suggest an alternative approach that combines rulemaking and guidance. Our approach takes into account the inherent flexibility of the systems-based QSR and the limitations of the current drug cGMPs for the regulation of combination products, and would allow appropriate and lawful regulation of a combination product as a whole under either regime.

SPECIFIC COMMENTS

We recommend modifying the guidance to correctly state the applicable legal requirements under the Act, as discussed above. There are also a number of places in the guidance where greater precision in describing the Act's legal requirements would be helpful. Further, because we are concerned that the guidance is unlawfully attempting to engraft specific drug cGMP requirements onto the QSR for drug/device combinations that are regulated as devices (and vice versa) without notice and comment rulemaking, we suggest an alternative approach.

- Section II.C describing "How are combination products regulated":
 - Second sentence, second paragraph, stating that "FDA will treat like products similarly": This merely states that FDA will follow the law. FDA should more specifically describe its interpretation of "like products" and "similarly", with examples. Fundamentally, combination products determined to be drugs, devices, or biologics should be subject to the cGMPs of that jurisdictional type. If that requirement of the Act is observed, similar products should be subject to the same basic cGMPs and any differences would have a legal foundation in the Act rather than be a matter of agency policy. For example, combination products that have complementary action and are made up of a drug product and finished device would be subject to QSR requirements for the device and cGMPs for the drug. This result is wholly consistent with the law.

- Section III.A describing the legal background of GMP regulations:
 - First paragraph describing the legal authority for drug and device GMPs: The description of legal authority here is somewhat misleading and glosses over the real differences between the drug cGMPs and the QSR. Section 501 alone does not create authority to promulgate cGMPs. Indeed, drug cGMPs were promulgated by relying on section 701 of the Act (generally authorizing FDA to promulgate regulations for the efficient enforcement of the Act) in combination with section 501. In contrast, device GMPs result from clear authority in the Act and its legislative history. *See* § 520(f)(1) of the Act (authorizing FDA to

prescribe regulations “requiring that the methods used in and that the facilities and controls used for, the manufacture, pre-production design validation (including a process to assess the performance of a device, but not including an evaluation of the safety or effectiveness of a device), packing, storage, and installation of a device conform to good manufacturing practice, as prescribed in such regulations, to assure that the device will be safe and effective and otherwise in compliance with this Act”).

Perhaps as a result, the drug cGMPs contain much more specific and prescriptive requirements to ensure the safety, quality, purity, identity and strength of drug products than the QSR, which takes a broader systems approach to ensuring quality that is less device-specific and can more readily subsume standards appropriate to drugs or biologics. The difference in the scope sections of the regulations demonstrates the difference in approach. Parts 210 and 211 “contain the minimum requirements” for cGMPs for drugs,⁷ whereas Part 820 “establishes basic requirements applicable to manufacturers of finished devices.” In fact, although the obligations of Part 820 are presumed, many of the regulations in Part 820 allow manufacturers leeway not to implement them “where appropriate”. For those regulations, if a manufacturer can justify (and document) that the requirement is inapplicable, it need not be implemented.

Thus, while drug cGMPs are limited in their flexibility, QSR design controls and purchasing and acceptance activities can provide cGMP requirements for drug/device or device/biologic combinations regulated as devices, without the need for the more prescriptive drug cGMPs requirements as contemplated in this draft guidance. As discussed above, the requirements applicable to the other jurisdictional types provide helpful guidance regarding the kinds of specifications the drug or biologic constituents should meet and the type of controls that are reliable in meeting them. However, alternative methods should also be acceptable to the agency under the QSR as long as the final combination device meets its specifications. Moreover, guidance that while not being prescriptive, is specific to QSR regulation of combination products that are devices, would be more helpful than guidance that simply attempts to engraft drug cGMPs onto the QSR.

We suggest that because the QSR has the inherent flexibility to provide standards for all constituents of combination products regulated as devices, without the need for further elaboration of legally enforceable requirements, the agency should consider notice and comment rulemaking to amend the drug cGMPs to make them more responsive to incorporation of QSR requirements (and biologic standards, blood cGMPs, and GTPs) for combination products regulated

⁷ Indeed, the summary section of the preamble to the 1978 final rule (amending the cGMPs to update them and “delineate requirements more specifically”) states that the update will make the regulations “more explicit and therefore less subject to varying interpretations, to assure that all members of the drug industry are aware of the level of performance expected of them to be in compliance with the act.” See 43 Fed. Reg. 45014 (Sep. 29, 1978).

as drugs. Until such a regulation is final, the preamble to the proposal could provide helpful guidance for drug and biologic manufacturers, and after the rulemaking is complete, the preamble to the final rule, and other guidance, would provide specific additional information in understanding FDA's new, enforceable requirements.

- Fourth paragraph and two succeeding bullets (providing examples of specific drug cGMP or QSR requirements that may only be more generally described in the other regulations): We agree that purposes of the drug cGMP and the QSR are similar, *i.e.*, to ensure manufacturers reproducibly make safe and effective and lawful products. However, as discussed above, the QSR is reasonably applicable to drug manufacturing without great stretching of language or interpretation, while the drug cGMPs are very specific to drug product manufacturing. For example, to the extent yield is critical to quality, strength, and purity specifications, the QSR would require it to be a manufacturing specification considered under design controls, and to be set, met, and audited under purchasing or processing controls or acceptance activities. In stark contrast, and contrary to the representation in the guidance, the QSR's corrective and preventive action requirements (CAPA) are not satisfactorily captured by drug cGMPs. The production record review regulation has no provisions for: corrective or preventive action; dissemination of information on the problems and corrections to responsible individuals; and managerial review. Under section 211.192, after an investigation, only documentation and "follow up" are required. "Follow up" constitutes an awfully vague standard for implementing a subsystem considered as crucial to quality control as CAPA. The agency's guidance *Quality System Approach to Pharmaceutical Current Good Manufacturing Practice Regulations* (September 2004) acknowledges that there is no provision for preventive action in the cGMPs, including 211.192. This section of the drug cGMP should be redrafted to acknowledge the significant differences between the systems as they currently exist. As discussed above, we believe notice and comment rulemaking should be initiated to increase the flexibility of the drug cGMPs so that they can comprehensively regulate combination products regulated as drugs or biologics.
- Section III.B, second paragraph, stating that for single entity or copackaged products both the drug cGMPs and QSR should apply: For the reasons discussed above, we disagree that individual cGMPs apply to constituent parts of combined or copackaged products. Where only one approval is necessary, only one set of cGMPs applies, those that apply to the jurisdictional identity of the combination product as a whole, *i.e.*, as a drug, device, or biologic. If a constituent part is separately legally marketed, then it must comply with the requirements applicable to its lawful status, *i.e.*, its status as a drug, device or biologic. In such instances, to the extent such a component of a combination product remains a finished device or drug product, continuing to apply the GMPs applicable to the product (if sold by itself) is appropriate, unless the

other constituent of the combination product provides the primary mode of action. In that case, the constituent would be legally subject to the GMPs of the product type that defines the combination product, notwithstanding that the combination may legally change the status of the constituent, for example, from a drug to a device component. Importantly, a constituent part of a combination product that is not a drug product or finished device will not be subject to cGMPs before it is accepted and integrated into the product. Instead, its specifications and acceptability would be set and assessed under the GMPs applicable to the combination product as a whole.

- Section III.B, third paragraph discussing the ease of complying with two sets of GMPs because of the overlap between the regulations: We believe that the agency is failing to follow the law and as a result is creating too much discretion to pick and choose applicable GMPs without legal authority. Specifically, by claiming that cGMP compliance can generally be achieved under either the drug cGMP or QSR regulations, FDA is acting without legal authority. Further, this paragraph ignores the cGMPs specifically applicable to biological products, including biologics establishment and product standards, specific cGMPs for blood establishments, and current standards for tissues and GTPs for HCT/Ps. While, as discussed above, we believe most if not all such standards can reasonably be accommodated to the extent appropriate to ensure product quality by the QSR,⁸ most cannot be reasonably integrated into a drug cGMP regime, they would be add-ons. Therefore, using rulemaking to liberalize the drug cGMPs is the lawful approach.
- Table 1 of the guidance specifying the specific drug cGMP and QSR requirements that would need to be integrated into the other regime for a drug device combination: This table illustrates the point that current drug cGMP requirements are very specific to drugs and that if drug cGMPs were to strictly apply to a device manufacturer who adds a drug constituent to his product, the manufacturer's quality system could require extensive modification. Indeed, device manufacturers are asked to "carefully consider" seven drug cGMP regulations not specifically covered by the QSR, whereas drug manufacturers only have to carefully consider three quality systems that may not be covered by their regulations.⁹ The guidance basically amends Part 820 in approach by making it more prescriptive and less systems-oriented, thus undermining the flexibility necessary for device manufacturers and potentially introducing compliance concerns resulting from FDA investigators having differing understandings of the QSR. The emphasis on specified drug cGMP provisions, rather than on the ability of device manufacturers to set specifications and procedures that will achieve the same goals under the QSR is contrary to the agency's overall stated goal of moving toward a risk-based quality system approach to products across the board.

⁸ Importantly, drugs and biologics that are intended for use in a combination product that is jurisdictionally a device are devices. See section 201(h) of the Act (components of or accessories to a device are a device).

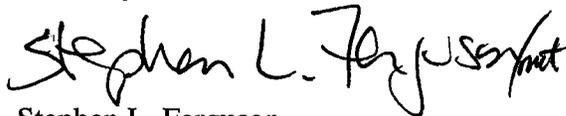
⁹ Nonetheless, a drug manufacturer would also have to modify significantly its cGMP operations, as the three subsystems listed in the table are among those considered most critical to the quality system regulation: design controls, purchasing controls, and CAPA.

- III.C, first bullet, second paragraph on requirements for single entity or co-packaged products: Here we have the same observation made above, the drug cGMPs and the QSR do not apply to component manufacturing, only to finished products.

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 revising this guidance. Unless a product constituent has an independent jurisdictional identity as a finished product, the jurisdictional identity of a combination product as a whole determines which GMPs apply, not the identity of the product constituents. Because those are the only GMPs that can be enforced under the Act, a multiple GMP approach to combination products is legally incorrect. We recommend that the agency initiate notice and comment rulemaking to enhance the applicability of drug cGMPs to combination products regulated as drugs. Because of the flexibility of the QSR, it does not require rulemaking to provide adequate GMPs for combination products; however, additional guidance regarding recommended standards for specific types of combination products under the QSR could be helpful.

Sincerely,



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