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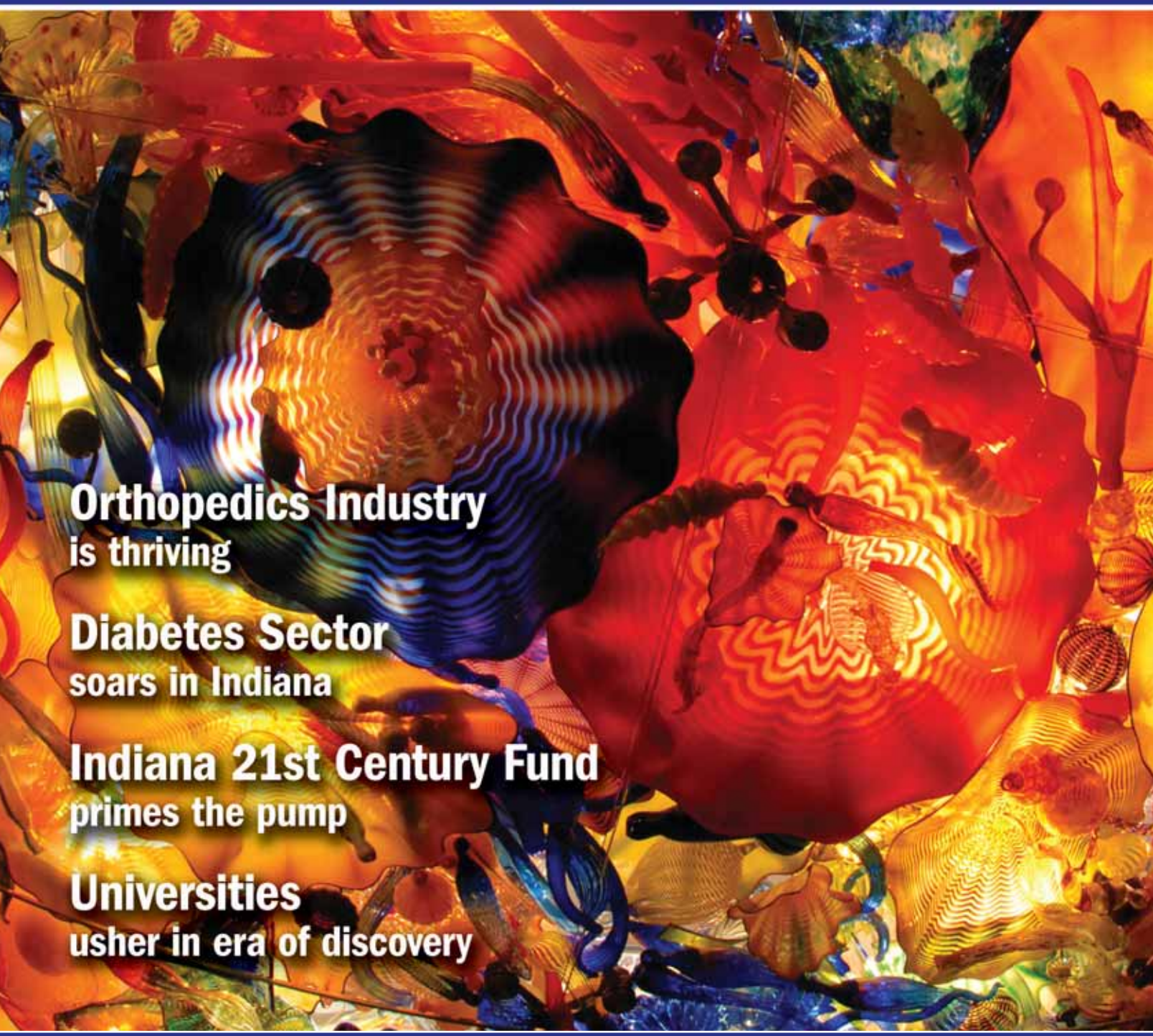

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Past, Present & Future: FDA regulation of combination products and GMPs

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Combination products — a product consisting of a drug/device, biological product/device, drug/biological product, or drug/device/biological product combination[1] – have become increasingly prevalent in the marketplace and important to patient care. Not surprisingly, because combination products are comprised of different FDA-regulated articles, the regulations that apply to combination products may involve different and conflicting regulatory frameworks. Since its establishment in December 2002, FDA's Office of Combination Products (OCP) has led the charge for clarifying and coordinating regulatory issues affecting combination products. One such issue is the application of Good Manufacturing Practices to combination products.

By way of background, Good Manufacturing Practices, or GMPs, refer to regulatory requirements that are intended to ensure that a product is not adulterated and possesses the quality, purity, strength, and other attributes that it is represented to have. The GMP regulations for drugs and most biological products are found at 21 C.F.R. Parts 210 and 211, for certain biological products at 21 C.F.R. Parts 600-680, and for devices at 21 C.F.R. Part 820.

September 2004 – Draft Guidance

FDA's official statements on the application of GMPs to combination products really began in September 2004, when OCP issued a draft guidance document on the subject. In addition to providing useful background on combination products and GMPs generally, the guidance document also sets the stage for FDA's current position with respect to GMPs and combination products. The guidance document articulates two important tenets for applying GMPs to combination products.

The first tenet is that as long as a constituent part (i.e., drug, device, or biological product) of a combination product remains separate from the product's other parts, that part is subject only to its own GMP regulations. By definition, some parts of a combination product remain physically separate during their manufacture and marketing. So under the guidance, the constituent parts of these products are subject only to the GMP regulations associated with that part. Also, for parts of a combination product that are eventually packaged, combined, or mixed together, before such packaging, combining, or mixing occurs, the parts of those products are also subject only to their respective GMP regulations. To take an example from the guidance, consider a photodynamic therapy system consisting of a laser and a photosensitizing drug that are manufactured and marketed separately. Under the first tenet, the laser is subject only to device GMPs while the photosensitizing drug is subject only to drug GMPs.

The second tenet is that after the constituent parts of a combination product are combined or packaged together, both sets of GMPs apply. Here, the guidance gives an example of a drug-coated device: Under the first tenet of the guidance, as long as the drug and device remain separate, the drug constituent part is subject only to the drug GMPs, while the device constituent part is subject only to the device GMPs. Once the drug and device constituent parts are combined, both sets of regulations apply to the combination product. Importantly, though, this second tenet does not require a manufacturer to implement two GMP systems. Rather, the guidance allows manufacturers to comply with both sets of regulations by using either set of GMPs. In other words, for the most part, manufacturers can achieve compliance "by using the [GMP] system already operating at a manufacturing facility . . . ." But there is a caveat to this rule.

The caveat is that the guidance recommends that manufacturers who co-package, combine, or mix constituent parts assess "how best to comply with both sets of regulations … by carefully considering the requirements of the [drug and device GMPs] in relation to the constituent parts, and the combination product(s) they manufacture." The guidance also offers advice on what the assessment should include and even identifies provisions that manufacturers particularly need to consider. This advice is of course very relevant for a manufacturer who is combining, mixing, or co-packing the constituent parts of a combination product.

June 2006 — Warning Letter

After the guidance document, FDA was relatively quiet about the application of GMP regulations to combination products until June 2006, when FDA issued a warning letter on the topic.[2] The warning letter arose out of an inspection of a medical device manufacturer by FDA's Los Angeles District. During the inspection, FDA also inspected certain corporate entities of the manufacturer that made drug-device combination products. The manufacturer asserted that these drug-device combination products were subject to regulation only under the device GMPs.

FDA disagreed and referred the manufacturer to the 2004 guidance, explaining that GMP regulations for both the drug and device constituent parts applied to the product. Further, though the letter acknowledged that compliance with both sets of GMP regulations can be primarily achieved by implementing just one set, FDA called the manufacturer's attention to the portions of the guidance that identify differing provisions of the GMP regulations. Like the guidance, the letter ultimately says that combination product manufactures should carefully consider these provisions to ensure full compliance with applicable GMP regulations.

This recent warning letter strongly suggests that FDA is proceeding with the regulatory pathways the guidance describes. This observation is also consistent with FDA's descriptions of the upcoming proposed rule on GMPs applicable to combination products, as described below.

Spring 2007 Proposed Rule

FDA is developing proposed regulations on GMPs for combination products, which are expected in Spring 2007.[3] FDA's descriptions of the upcoming proposed rule are consistent with the approach the guidance document and warning letter describe. For example, as recently as December 2006, FDA described the proposed regulations as providing a framework under which compliance with a manufacturer's existing GMP system, or one that the manufacturer selects, will generally meet the requirements of the other applicable set of GMP regulations. For example, application of the drug GMP regulations will "generally meet the requirements" of those for devices. Importantly, though, as in the guidance and warning letter, FDA has been careful to mention that a manufacturer's system will also need to incorporate "select, key provisions from the regulations pertaining to the other part of their combination product."[4]

In sum, while there's always the possibility of surprises when FDA publishes the proposed rule, the recent warning letter and FDA's descriptions of the impending proposed rule suggest that the approach will be substantially similar to the September 2004 guidance document. This approach should offer a flexible framework for manufacturers and for the most part should allow them to continue to operate under their existing GMP systems. •

1 *21 C.F.R. § 3.2(e).*

2 *FDA, Los Angeles District Office, Letter to P.Porteous, Dux Industries (June 1, 2006).*

3 *71 Fed. Reg. 73196, 73221 Regulatory Agenda (Dec. 11, 2006).*

4 *Id.; see also FDA, Current Good Manufacturing Practice for Combination Products, Presentation by J.Cohen given at AdvaMed Medical Technology Learning Institute Conference (May 25, 2006).*