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Practical Solutions for Handling the Sale of Patient-Specific Devices in the USA

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UNDERSTANDING THE US FDA'S CUSTOM DEVICE EXEMPTION

Practical Solutions for Handling the Sale of Patient-Specific Devices in the USA

With the ever-increasing sophistication of medical technologies, patients and physicians alike are looking for more personalised solutions for addressing medical problems. In the face of this market demand for personalised medicine, medical device companies are increasingly seeking to manufacture and market devices that are tailored to address a specific patient's needs. This is particularly true in the world of implantable reconstructive and orthopaedic devices, where physicians and patients are seeking implants that are tailor-made to match each patient's anatomy.

The trend toward personalised medicine, including personalised medical devices, has created new challenges for both regulators and manufacturers. Also, with the US Food and Drug Administration's (FDA's) increased focus on enforcement since the appointment of Margaret Hamburg, MD as Commissioner[1], it is a good time for device manufacturers to revisit their procedures for the manufacture and sale of custom devices.

This article seeks to remind device manufacturers of the FDA's definition of custom devices, and the Agency's interpretation of that regulation; to help manufacturers recognise what a custom device is, and what it is not; and to set forth recommendations for avoiding common custom device pitfalls and FDA enforcement actions.

What is a 'custom device'?

The *Federal Food, Drug and Cosmetic Act* (FFD&C Act) prohibits the introduction of any adulterated device[2] into interstate commerce, with two exemptions: the investigational device exemption (IDE) and the custom device exemption. IDE approval allows an adulterated device to be distributed as part of a clinical investigation if certain conditions are met[3]. Similarly, under Section 520(b) of the FFD&C Act[4], custom devices are exempt from the performance standards, pre-market clearance and approval, and IDE requirements, but not the FDA's Quality System Regulations. In Title 21 of the Code of Federal Regulations (21 CFR) Section 812.3(b), the FDA defines 'custom device' as a device that:

- necessarily deviates from devices generally available or from an applicable performance or pre-market approval (PMA) requirement in order to comply with the order of an individual physician or dentist;
- is not generally available to, or generally used by, other physicians or dentists;
- is not generally available in finished form for purchase or for dispensing upon prescription;
- is not offered for commercial distribution through labelling or advertising; *and*
- is intended for use by an individual patient named in the order of a physician or dentist, and is to be made in a specific form for that patient, or is intended to meet the special needs of the physician or dentist in the course of professional practice.

Although the definition of a custom device is clearly set forth in FDA law and regulation, interpretation of this definition is anything but clear. A number of manufacturers who have called their devices 'custom devices' have received warning letters indicating that their product does not meet the FDA's regulatory definition of a custom device[5]. Today, the FDA very narrowly interprets the definition of a custom device to mean that it is virtually 'one-of-a-kind'[6]. In the spirit of this narrow construction, the

FDA typically takes the position that a custom device is unique and crafted specifically for an individual patient or physician. However, as discussed in greater detail below, the simple fact that a device is unique is not enough to meet the definition of a custom device. When determining whether a device meets the definition of a custom device, it is important to make this assessment in the context of whether the device is more appropriately characterised as 'custom' or 'customised'. The discussion that follows is intended to shed some light on this distinction, as well as the proper interpretation of each of the five bullet points of the custom device regulation set forth in 21 CFR Section 812.3(b) (*see above*).

Point 1: necessarily deviates from devices generally available or from an applicable performance or pre-market approval requirement in order to comply with the order of an individual physician or dentist

The FDA believes that the 'necessarily deviates' requirement for a custom device means that the device is 'sufficiently unique that clinical investigations would be impracticable'[7]. In keeping with this interpretation, the Agency has indicated that contact lenses ordered specifically for a named patient on the basis of a prescription do not satisfy the definition of a custom device because, among other things, clinical investigations of contact lenses are practicable[7].

Contact lenses may be more appropriately considered customised devices. A customised device is a device that is widely disseminated but can vary in size, shape or material on the order of a physician to meet the needs of an individual patient. The FDA's regulations effectively exclude customised devices from the definition of a custom device and, therefore, customised devices are subject to the FDA's pre-market approval or clearance requirements, including the requirement for adequate labelling. For example, Align Technology, Inc., markets Invisalign®, a series of removable orthodontic appliances that are specifically customised for each patient, on the basis of a cleared pre-market notification (510(k)) (K981095). With Invisalign®, the treating orthodontist or dentist writes a prescription for each patient based upon the patient's initial orthodontic condition and the desired treatment outcome, and Align Technology, Inc. fabricates a set of aligners for each patient based on that patient's individual characteristics. The aligners are available for sale through prescription, widely advertised (through the Internet, trade press, radio and television advertisements), and are generally available to orthodontists and dentists for use.

Similarly, Polyclinic Medical Center's hard tissue replacement - patient match implant (K924935) is 510(k) cleared for use in 'craniofacial procedures for augmentation and reconstruction'. According to its 510(k) summary, this product is 'an exact-fit implant based on the patient's craniofacial geometry' that is 'designed specific [sic] for each patient', 'will maintain its shape after implantation', and 'provides for replacement of an amorphous shaped implant not contained within standard product lines'. The 510(k) summary also states that the product is designed and moulded for a specific patient to fill defects in the craniofacial bones. Although this device is patient-specific, it is not a custom device; rather, it is better described as a customised device.

Customised implants are typically manufactured to fit the specific anatomy of each patient using computed tomography scans of the patient's anatomy, or are assembled from components that fall within a 510(k)-cleared range of sizes. Although these devices are made in a specific form for each patient, the devices are not appropriate for exemption from pre-market notification or approval, as the processes used to manufacture these devices can be validated, and the resulting implants feasibly can be studied and need not deviate from specified performance criteria. In short, experts in the field conclude that devices resulting from a company's project

development plans - regardless of whether or not those devices are tailored to a specific patient - are unlikely to meet the definition of a custom device[8].

In early 2000, the FDA stated that it intended to develop a guidance document to clarify its interpretation of the custom device regulation. Although it has not issued any such guidance to date, the Agency indicated at the time of that statement that it was not likely to take enforcement action if the number of custom devices distributed was less than the number needed to conduct a feasibility study (e.g. less than five per year)[9]. In other statements, the FDA has indicated that a company may make as many as 10 devices per year without fear of FDA enforcement action[10]. However, in contradiction to its informal statements, the FDA indicated in a 20 July 2003 warning letter to Inter-OS Technologies, Inc. that the company's dental implants were not custom devices, in part because two patients 'received implants of the same prototype'. Specifically, the FDA stated:

> 'Custom devices are intended for use by an individual patient named in a dentist or physician's order and made in a special form for that patient. Two patients received implants of the same prototype [redacted] device. Although you customized the device to fit each patient, the [redacted] was the same design and not made specifically for each patient'.

As demonstrated by the above statements, a proper assessment of each proposed custom device according to the statutory definition cannot be substituted with a simple quota, regardless of how small. The mere fact that a small number of devices, or even a single device, is manufactured does not necessarily mean that the device may be sold as a custom device.

Point 2: is not generally available to, or generally used by, other physicians or dentists

If a specific device is generally available to or used by other physicians or dentists, it cannot be a custom device. In other words, if the features of a device fall within a range of features that are commercially available to a physician, regardless of the manufacturer, the device itself cannot be sold as a custom device. In keeping with the FDA's view that a customised device is not a custom device, for example, the FDA considers a prescription contact lens to be 'generally available' if it is merely a variation within a range of powers and anterior and posterior surface contours that other doctors could purchase for their patients. This position was affirmed by the US Court of Appeals for the District of Columbia in its 1985 opinion in Contact Lens Manufacturers Association versus the FDA[11]. That case was one of the first involving an attempt to reclassify a medical device that had been automatically classified into Class III and remains one of the few court cases to discuss custom devices. In that case, the Contact Lens Manufacturers Association maintained that the devices at issue - rigid gas permeable contact lenses - were custom devices, as defined in the FFD&C Act. In its opinion, the court considered a list of custom devices described in the House Report accompanying the passage of the custom device requirements, which included orthopaedic and other prosthetic devices, dental devices and specially-designed orthopaedic footwear. The court rejected the argument that rigid gas permeable contact lenses are custom devices, finding that a given contact lens 'is merely a variation within an approved range of powers and anterior and posterior surface contours'. Under the definition of a custom device, anything that is likely to be replicated again and again is 'generally used' or 'generally available' under the statute.

Point 3: is not generally available in finished form for purchase or for dispensing upon prescription

If a given device is sold in sufficient quantities that it becomes commercialised, the FDA will consider the device to be 'generally available', and thus ineligible for the custom device exemption. This

interpretation is supported by the FDA's warning letter to Wright Medical Technology, Inc., dated 1 December 1999, indicating that the company's CONSERVE® PLUS hip prosthesis was not a custom device. Although not the primary reason for its conclusion that the CONSERVE® PLUS was not a custom device, in support of its decision, the FDA noted that the company shipped multiple devices of the same size, made multiple shipments to the same physician, and shipped large numbers of CONSERVE® devices or components[11]. That multiple shipments of several devices of the same size were shipped to the requesting physician suggests that these devices were commercialised, and therefore generally available in finished form. (This warning letter and the FDA's ultimate reasons for its determination are further addressed in the discussion of Point 5 *below*.)

Given that repeatedly manufacturing the same device may be considered enough to commercialise that device, it is important for companies to avoid producing sufficient quantities of a custom device to commercialise it. One approach is to establish a limit on the number of units of a device that may be manufactured and sold under the custom device exemption. This approach is not risk free, however, as to qualify for the custom device exemption it is not enough that a device is manufactured in small quantities - particularly in light of inconsistent statements by the FDA on this topic and the Agency's current interpretation of the definition of a custom device. However, the establishment of such a limit may serve as an internal check on the company's custom device activities, and may signal the need to consider a new regulatory submission for certain devices.

Even for companies who establish a maximum number of times a custom device may be manufactured, knowing when the device may have become commercialised may be difficult. First, it is often difficult to determine what makes a device the 'same' as one that was previously sold. Do the specifications of the device have to be exactly the same, or are some differences so minimal that they do not actually amount to a 'different' device? Is there a material difference between sizes 0.10 and 0.101? There is no easy answer to these questions, except to say that the determination will depend on the nature of the devices, their similarities and differences, and the level of regulatory risk that the company is willing to accept. Second, the company's intent can be a factor in the FDA's assessment of its custom device activities. For example, if the numbers and types of devices manufactured as custom devices suggest that the company is trying to circumvent the FDA's pre-market approval or clearance requirements, the Agency is likely to object to the sale of devices under the custom device exemption. On the other hand, if a manufacturer appears to be truly offering custom devices only in rare cases where use of the exemption is truly warranted, the FDA is likely to be more tolerant. Thus, it is important for a company to have a solid, written justification explaining why each device sold under the custom device exemption meets the regulatory definition for a custom device.

In determining whether a device is 'generally available in finished form' it is also important that device companies consider whether a commercially-available product from another manufacturer could meet the patient's or physician's needs. If such a product is available, the FDA is likely to consider the subject device to be 'generally available' because, as discussed above, the Agency is particularly concerned about the use of the custom device exemption as a shortcut around its pre-market approval or clearance requirements. From the Agency's perspective, it is always better to use a device that has been scrutinised via the pre-market approval or clearance process (if available), rather than a custom device that has not undergone such scrutiny. Furthermore, the FDA does not agree that a hospital, physician or patient preference for a 'one-off' device from a certain, preferred manufacturer, rather than a similar, commercialised

device from another manufacturer is sufficient to justify the sale of a device under the custom device exemption. This position was expressly stated in the Agency's 2 July 2004 warning letter to Archibald S Miller, II, MD, FACS, in which the FDA took the position that the breast implants implanted by Dr Miller were not custom devices. That letter states:

> 'In fact, there are saline-filled mammary implants currently available for breast augmentation in women 18 years or older and for breast reconstruction in women of all ages…The custom device provision was not meant to allow the circumvention of otherwise applicable provisions under the Act'.

As with the Wright Medical letter discussed above, the FDA's ultimate determination (discussed under Point 5 *below*) was that the devices were not made in a 'specific form' for a named patient; however, the language quoted above also suggests that the commercial availability of similar devices precludes the sale of a device pursuant to the custom device exemption.

Point 4: is not offered for commercial distribution through labelling or advertising

Although the fact that a device is not advertised, promoted or labelled is not dispositive of its status as a custom device, a device that is advertised, promoted or otherwise 'offered for commercial distribution through labeling' cannot be sold as a custom device. Under Section 201(m) of the FFD&C Act, labelling is a broad term that encompasses device labels as well as 'all other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article'[12].

The FDA and the courts interpret 'accompanying' quite broadly to mean material that is not only physically provided along with the device, such as the Instructions for Use, but also material that does not physically accompany the device but is part of an integrated sales transaction or is offered in conjunction with the device for the purpose of providing an explanation of the device. Clinical study summaries, white papers, trade show exhibits, mailings, case studies, press kits, flyers, booklets, price lists and training materials have all been construed as medical device labelling. Accordingly, if a device is featured or discussed in any of the above or similar materials, the FDA is likely to take the position that the device is offered through labelling and does not meet the definition of a custom device. Furthermore, although promotion of a company's ability to produce custom devices is not *per se* prohibited, depending on the nature and extent of such promotion, it could be enough to draw an enforcement action from the FDA. For example, if a company promotes its ability to manufacture specific types of custom devices, publishes a catalogue of custom devices, or includes examples of devices previously sold as custom devices in its promotional material, the FDA could consider this enough to disqualify any device manufactured by the company from meeting this point of the custom device exemption.

While FDA guidance on custom devices has been sparse in recent years, the issue of whether a company was properly selling custom devices was the subject of recent US case law. In the 30 March 2009 case of the United States versus Endotec, Inc.[13], the US Court of Appeals for the Eleventh Circuit considered the issue of whether certain implantable medical devices (including knee, ankle and temporomandibular joint implants) manufactured and distributed by Endotec, Inc., were 'custom devices' within the meaning of the FFD&C Act. The court held that the manufacturer, who alleged that the devices in question were custom devices and thus exempt from pre-market notification or approval requirements, bore the burden of proving that the devices fell within the custom device exemption. To determine whether this burden was met, the court used the definition for a custom device set forth in 21 CFR Section 812.3 (*see above*).

Notably, the court stated that the definition for custom device does not require any showing of danger or actual harm from the government.

The court found that because Endotec's advertisements explicitly referred to 'Endotec customs' and further characterised the company's custom ankle devices as the company's 'specialty', and because the co-owner's private practice website advertised implantation of the company's ankle device, which was implanted only as a 'surgeon special', the devices in question failed to meet the fourth point of the custom device definition (i.e. not offered for commercial distribution through labelling or advertising). Although Endotec claimed that these advertisements were nothing more than disclaimers that the products were for custom use, the court rejected the company's justification. As the custom device definition requires all five points to be met, the court held that the ankle devices were not custom devices within the meaning of the FFD&C Act and declined to address the remaining points.

Point 5: is intended for use by an individual patient named in the order of a physician or dentist, and is to be made in a specific form for that patient, or is intended to meet the special needs of the physician or dentist in the course of professional practice

As the terms 'specific form' and 'special needs' are so vague, the FDA has broad discretion in interpreting them. As a result, the FDA often bases its determination that a device is not a custom device solely on the patient-specific form/physician special need criterion. For example, the FDA's warning letter to Archibald S Miller, dated 2 July 2004 and discussed above, concluded that the breast implants that were being used by Dr Miller in a clinical study (the device's name was redacted from the warning letter because it is an investigational product) were not custom devices, and they were not the subject of an approved IDE. In that letter, the FDA stated that:

> 'The [redacted] distributed by [redacted] and developed by you do not meet the criteria for a custom device and, therefore, are not exempt from compliance with the premarket approval or investigational device exemption regulations. For example, these mammary implants are not intended for use by an individual patient named in a physician's order and made in a specific form for that patient…In fact, there are saline-filled mammary implants currently available for breast augmentation in women 18 years or older and for breast reconstruction in women of all ages…The custom device provision was not meant to allow the circumvention of otherwise applicable provisions under the Act'.

Thus, a given device is not considered to be made in a 'specific form' for an individual patient - one of two alternative requirements in the fifth point of the custom device definition - if a similar product is commercially available. Thus, as discussed with respect to Point 3 above, commercialisation of a device, regardless of the commercialising company, can violate a number of points of the custom device definition. In fact, arguably, it would be enough to violate all five points if correctly assessed in light of the FDA's prior enforcement actions.

Many of the warning letters regarding custom devices have involved orthopaedic devices. This focus on orthopaedic devices is not surprising because it is a common practice in the orthopaedics industry to 'individualise' devices for specific patients to fit their skeletal features. In its warning letters, however, the FDA has taken the position that such patient-specific devices are not custom devices because they are not made in a 'specific form' for an individual patient or meet a 'special need' of a physician, even if they are intended for specific patients or for certain physicians. For example, in its 1 December 1999 warning letter to Wright Medical Technology, Inc., the FDA addressed the alternative requirement that devices be intended to meet the 'special need' of a physician or dentist to be a custom device. In that letter, the

FDA indicated that Wright's CONSERVE® PLUS hip prosthesis was not a custom device because:

> 'A custom device, among other things, must be intended for use by an individual patient named in a prescription or be intended to meet the special needs of a physician in the course of their professional practice. The Conserve PLUS is neither intended for use by an individual patient nor is it intended to meet the special needs of an individual physician in the course of his professional practice. A special need is a need that is unique to the physician as an individual. A device that meets a need that is shared by others in the field, and is not unique to them as individuals, is not a special need. A device that meets a need that is shared by others in the field can be tested through clinical investigations and can be subject to the PMA requirements in order to ensure that it is safe and effective, and is not a custom device'.

The FDA further clarified that a 'special need is one that relates to the unusual anatomical features of the individual physician for whom the device is produced, or to special needs of his or her practice that are not shared by other health professionals of the same specialty' in a 15 March 2002 warning letter to Endotec, Inc. Thus, the 2002 Endotec warning letter further clarifies that a device must meet the specific needs of an individual physician, and not just the needs of the physician who has a certain medical specialty, to satisfy that alternative requirement.

So what is a custom device?

Unfortunately for industry, the Endotec court case ruled that the company's ankle implants were not custom devices largely on one factor: that those devices had been advertised and thus did not meet the definition of a custom device, which requires that all five points be satisfied. In doing so, the court avoided a detailed discussion of the remaining four points, which would have provided much-needed guidance to industry. However, the Endotec case did affirm that the company's temporomandibular joint implant, which was specifically made for a cancer patient who was missing a large piece of bone in her jaw, was a custom device[13]. This ruling provides industry with a scarce example of what actually does meet the regulatory definition of a custom device.

Recommendations

If the FDA disagrees with a company's assessment that a device is appropriately sold as a custom device, the Agency can require the company to submit a 510(k) notice or PMA application for the device, issue a warning letter to the company, require the recall of the so-called custom device, and take other regulatory or enforcement action against the company. In light of the risk presented by the manufacture and sale of custom devices, companies should seek to avoid reliance on the custom device regulation whenever possible. To do so, manufacturers should consider the following recommendations:

- Establish a 'triage' procedure to handle incoming requests for one-off or patient-specific medical devices. This procedure should guide company personnel through an assessment of whether (in order of regulatory preference) the requested device:
  - falls squarely within one of the company's 510(k) clearances or PMA approvals;
  - requires clearance of a new 510(k) or approval of a PMA or PMA supplement;
  - is the type of modification to a 510(k)-cleared device that is appropriate for implementation on the basis of internal documentation (i.e. memorandum to file)[14];
  - falls within a 510(k)-exempt product classification; *or*
  - meets all of the points of the definition of a custom device.

In light of the regulatory uncertainty posed by

the custom device exemption, and of the FDA's strict interpretation of the regulation to essentially mean a one-of-a-kind device, companies would do well to avoid the use of this exemption where uncertainty exists.

- Establish a custom device procedure that, among other things, requires the company to document its determination that a given device meets the definition of a custom device. Such documentation may be helpful in defending the company's position that a device meets the definition of a custom device. Alternatively, such documentation may help to secure the Agency's enforcement discretion should the FDA take the position that the subject device does not qualify for the custom device exemption.
- Seek broad 510(k) clearances and PMA approvals that describe a range of products or product features (e.g. sizes, powers) that can be manufactured, sold and marketed pursuant to that clearance or approval. For example, companies can seek 510(k) clearance for a range of device sizes (e.g. 1-10 cm) that can be supplied, rather than identifying each specific size that is available (e.g. 1, 3, 7 and 10 cm). In the first case, a request for a 5 cm device would fall squarely within the range of the cleared products, while in the second, a 5 cm device would be outside the scope of the clearance, forcing the company to:
  - decline the request;
  - file a new 510(k) for a 5 cm device;
  - determine whether the change can be implemented via internal documentation; *or*
  - manufacture the size 5 as a custom device, if all the criteria are met.
- Seek 510(k) clearances or PMA approvals that describe the process undertaken to manufacture products that are tailored to each patient's specific anatomy. Such an approach is consistent with the idea of 'customised' devices, similar to Invisalign®, and would allow the company to manufacture custom-made or patient-specific devices in a way that avoids the regulatory uncertainty posed by the Agency's custom device regulation.
- For existing devices with specific 510(k)-cleared dimensions, when a request for a dimension that falls within the range of 510(k)-cleared dimensions (e.g. 5, when 3 and 7 are cleared dimensions), or are very close to those dimensions (e.g. 10.1, when 10 is the largest cleared dimension), the company should assess whether making the requested product size could significantly affect the safety or effectiveness of the device, or represent a major change to the intended use of the device. If the answer is no, the company reasonably could provide the requested size on the basis of internal documentation (i.e. memorandum to file), rather than as a custom device. Under this approach, the company would then be able to market additional units of that size, as it would then be within the scope of the subject 510(k).
- For certain other devices that are not the subject of a cleared 510(k) or approved PMA, the company should consider whether the devices can appropriately be characterised as Class I, 510(k)-exempt devices (e.g. general surgical tools), which may be marketed without 510(k) clearance or PMA approval, if the device falls within the limitations of the exemption (*see*, for example, 21 CFR Section 878.9).
- If the company is unsure whether a product can appropriately be sold as a custom device, it can always seek an informal opinion from the FDA's review staff. While such opinions are not binding on the Agency, they can be a useful sanity check for the company. In the author's experience, however, while the predictive value of a positive informal response from Agency staff is not particularly high, if the informal response is in the negative, the FDA is likely to take the position that the device does not qualify for the custom device exemption.

- For products that are not 510(k)-exempt and that cannot be marketed pursuant to PMA approval, 510(k) clearance or a memorandum to file, as described above, it may be appropriate for medical device companies to manufacture and sell these products as custom devices. However, companies should ensure that each product that is sold as a custom device meets the regulatory definition of a custom device, in light of the above discussion, and should document the justification for its decision in its regulatory files.

References

1. Remarks by Margaret A Hamburg, MD, Commissioner of Food and Drugs on *Effective Enforcement and Benefits to Public Health* at the Food and Drug Law Institute, 6 August 2009.
2. 21 United States Code (USC) §331(a) and (k).
3. 21 CFR Section 812.
4. 21 USC 360j(b).
5. For example, warning letter to Kremer Eye Associates (1995), warning letter to Pudenz-Schulte Medical (1995), warning letter to Respironics, Inc. (1994), warning letter to Medtronic Biomedicus (1994), warning letter to Geneva Laboratories, Inc. (1994), warning letter to Dental Health Products, Inc. (1994), warning letter to Med, Inc. (1993), and warning letter to Orentreich Medical Group (1991).
6. 21 USC §360j(b), the statutory provision that establishes the custom device exemption, states: 'Sections 360d and 360e of this title do not apply to any device which, in order to comply with the order of an individual physician or dentist…necessarily deviates from an otherwise applicable performance standard or requirement…if (1) the device is not generally available in finished form for purchase or for dispensing upon prescription and is not offered through labeling or advertising by the manufacturer, importer, or distributor thereof for commercial distribution, and (2) such device -
(A)(i) is intended for use by an individual patient named in such order of such physician or dentist…and is to be made in a specific form for such patient, or
(ii) is intended to meet the special needs of such physician or dentist…in the course of the professional practice of such physician or dentist…, and
(B) is not generally available to or generally used by other physicians or dentists'.
7. *Federal Register*, 1983, **48**, 56778 and 56796 (23 December 1983).
8. *FDA Wins Injunction Against Endotec 'Custom' Ankles And Knees*, *The Gray Sheet*, 20 April 2009.
9. *Draft Guidance Clarifying Custom Device Criteria to be Released in Spring*, *The Gray Sheet*, 28 February 2000.
10. *FDLI Annual Conference In Brief*, *The Gray Sheet*, 26 April 2004.
11. Contact Lens Manufacturers Association versus the FDA, 766 F.2d 592, 599 (District of Columbia Circuit 1985).
12. 21 USC §321(m).
13. United States versus Endotec, Inc., 563 F.3d 1187, 1204 (11th Circuit 2009).
14. FDA's standard for when a modification to a 510(k)-cleared device may be made without the need to file a new 510(k) notice is whether the change could significantly affect the safety or effectiveness of the device, or represents a major change to the intended use of the device. *See* FDA's Guidance Document entitled *Deciding When to Submit a 510(k) for a Change to an Existing Device* (10 January 1997).

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