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NO SUMMER VACATION FOR DEVICE REGULATORS: AN OVERVIEW OF RECENT LEGISLATION AND FDA ACTIVITY, PART I

Over the summer, Congress enacted new laws regulating medical devices. The highlight of the legislation was the Medical Device User Fee Amendments of 2012 ("MDUFA"). However, these amendments were just a small part of the Food and Drug Administration Safety and Innovation Act ("FDASIA"), which made dozens of changes to the Food, Drug, and Cosmetic Act.[1] In addition to these legislative changes, the Food and Drug Administration ("FDA") issued its own set of regulations and guidance documents, and in consideration for an extension by Congress of the user fee program, the FDA committed publicly to a lengthy list of goals, which should be read against the backdrop of this new legislation.

In this *Commentary*, presented in two parts, we summarize the new legislation and the FDA's goals and regulations. In this Part I, we address the user fee provisions for applicants and registrants and the program's complementary "MDUFA III Commitment Letter," wherein the FDA set forth its performance goals. We describe developments affecting establishment registrations, investigational device exemptions ("IDEs"), clinical trials, premarket approval applications ("PMAs"), 510(k) submissions, and certain post-approval obligations.

In Part II, presented in a separate publication, we outline the new unique device identifier ("UDI") proposed rules and other related FDA initiatives, and we highlight where the FDASIA amendments intersect with the FDA's goals. We also discuss some of the special amendments, like those that address humanitarian and custom devices, and relate to accredited persons who have the power to assist the FDA with inspections and applications.

USER FEES AND THE MDUFA COMMITMENT LETTER

User fees are imposed for a variety of applications, and on establishment registrations. The user fee program itself is not new. Rather, Congress merely extended the program for another five years.[2] Fees will continue to be assessed for a broad range of filings, including PMAs and establishment registrations. And, as before, the funds generated from user fees will fund the FDA's review of device applications.[3] A full schedule of fees appears in the Federal Register.[4]

Applications Fees. In addition to its basic reauthorization of the user fee program, Congress has legislated a continuum of fee increases through 2017. To provide a baseline, fees for PMAs in fiscal year 2012 were $220,050.[5] In 2013, however, they will rise to $248,000,[6] and they will continue to rise each year. Subject to adjustments, user fees for PMAs will ultimately be $268,443 in 2017.[7]

While fee increases obviously translate into rising costs for businesses, there is some available relief. First, the new legislation retained existing provisions that allow reduced fees for small businesses and a waiver of fees for their first PMA or report.[8] Second, fee waivers are available for certain submissions including those related to humanitarian devices, devices licensed for further manufacturing use only, devices marketed solely for pediatric populations, submissions with government sponsors, and those made to "accredited persons."[9] Now, and in addition to these enumerated aids, the FDASIA provides the FDA with broad discretion to reduce or waive fees when doing so "is in the interest of public health."[10] However, seeking this type of relief could delay the application process. While the FDA is committed to meeting specified timetables for responding to most submissions, it makes no such commitment regarding applications that receive "in the interest of public health" fee reductions or waivers. Rather, such applications "shall be reviewed by the Agency as resources permit."[11]

Registration Fees and Expanded Registration Requirements. Congress also increased fees associated with registering a manufacturing establishment. This registration fee, currently set at $2,029 for fiscal year 2012,[12] will rise each year, starting in fiscal year 2013 ($2,575) and, subject to adjustments, will ultimately be $3,872 in fiscal year 2017.[13] As with application fees, the FDA can waive registration fees "in the interest of public health." However, the other enumerated reductions and waivers permitted against applications fees are inapplicable to registration fees.[14]

In addition, more establishments are now required to register and pay fees. Specifically, as a result of a new regulation, previously exempt contract manufacturers, and manufacturers that sterilize or make sterilized devices to another manufacturer's specifications, are now required to register.[15] And, under the FDASIA, every establishment that is "registered (or is required to register) … because such establishment is engaged in the manufacture, preparation, propagation, compounding, or processing of a device" will be required to pay a registration fee.[16]

Congress also strengthened the FDA's power to enforce the registration requirement upon foreign facilities. While foreign facilities were already subject to registration,[17] before the FDASIA, their failure to register did not render their device "misbranded" unless the device was manufactured "in any State."[18] Now, both imported and domestic devices will be deemed "misbranded" unless the manufacturing establishment is properly registered.[19]

One related administrative point should be mentioned here. Registration now may be completed only via the FDA Unified Registration and Listing System ("FURLS") on the internet. Specifically, on August 2, 2012, the FDA implemented a new rule requiring all registrants to complete their applications through FURLS.[20] The rule also adds a number of technical requirements governing what information must be provided during registration, including an e-mail and web address.[21]

The MDUFA III Commitment Letter and FDA Performance Goals. In exchange for the retention of and increases in user fees, the FDA adopted numerous performance goals, which are set forth in a letter to Congress known as the "MDUFA III Commitment Letter."[22] While these "goals" are not mandated by regulation, the FDA is required to provide Congress with periodic reports documenting its progress.[23]

The initial part of the FDA's Commitment Letter contains a series of process improvement goals, including

pre-submission process improvements, revisions to submission acceptance criteria, and an interactive review process. Generally, the FDA plans to improve its guidance process by deleting obsolete guidance documents and by setting out its priorities for developing further directives. To this end, the FDA has already issued some guidance documents on its contemplated improvements, including drafts regarding the pre-submission program and the acceptance process for 510(k) and PMA submissions (which are discussed below).

In addition to guidance-related goals, the FDA expressed its intent to support a third-party review program (making it more transparent), and to provide more insight on how it makes certain benefit-risk determinations. The FDA also plans to exempt more low-risk devices from premarket notification, and it intends to develop a "transitional" in vitro diagnostics approach for the regulation of emerging diagnostics.

The core of the Commitment Letter, however, contains detailed timetables designed to promote the FDA's primary goal of reducing review times for a variety of submissions. For example, for submissions made in fiscal year 2013, the FDA aims to have the total time to decision average 395 calendar days for PMAs and 135 calendar days for 510(k) s. Other timetables relate to intermediate milestones in the regulatory process and decision times for various other submissions. The proposed timetables are designed to become tighter in future years, calling for faster average turnarounds, higher percentages of submissions timely resolved, and better communications with applicants throughout the decision-making progress.

Some of the other pledges in the FDA's Commitment Letter include plans to hire more reviewers, improve reviewer training, make better use of external experts, and develop a tracking system that will provide real-time status information for submissions. The FDA also pledged to develop a comprehensive assessment of the review process, which will be accomplished in conjunction with the medical device industry. The goal of this assessment is to identify best practices, eliminate inefficiencies, analyze the FDA's collection of information and reporting processes, and make recommendations for further study. Only time will reveal whether the FDA's goals are met and to what degree and effectiveness. The industry, of course, will be watching closely.

CLINICAL TRIALS AND INVESTIGATIONAL DEVICE EXEMPTIONS

Clinical trials and applications for IDEs are clearly subject to FDA oversight and control. However, new provisions in the FDASIA curb this power in some ways, yet expand it in others.

Disapproval of an IDE—Reporting Requirements. The FDA has always had the power to disapprove an IDE application where the investigation does not conform to applicable regulations.[24] While this remains true, Congress clarified that the FDA may not disapprove an IDE merely because it is not sufficient to support the device's eventual approval or clearance or would not support a substantial equivalence or *de novo* classification of the device.[25] Furthermore, while the FDA continues to have the power to require investigators to submit extensive reports,[26] the FDASIA specifies that this power extends only to demands for "safety or efficacy data."[27]

IDE Clinical Holds. While the FDASIA restricted the FDA's authority to disapprove IDEs, the FDASIA granted the FDA a new power—authority to place an IDE investigation on a clinical hold (and thereby prohibit the sponsor from continuing the investigation).[28] This new clinical hold provision is substantively identical to the provision governing holds on clinical trials of drugs[29] and is in addition to the FDA's existing power to withdraw an IDE.[30] Simply stated, the FDA may now impose a clinical hold if an investigation presents "an unreasonable risk" to the test subjects.

This power is not without limits. If a sponsor asks the FDA to remove the clinical hold, the FDA must decide within 30 days whether to grant that request, and the FDA must specify the reasons for its decision.[31]

Foreign Clinical Trials and IDEs. The FDASIA also addresses foreign clinical trials. Under existing regulations, studies conducted in foreign countries could support PMAs if they were conducted under an IDE submitted to the FDA, or "if the data are valid."[32] An additional regulatory provision requires that such studies be conducted in accordance with either the law of the host country or the Declaration of Helsinki, "whichever accords greater protection to the human subjects."[33]

The FDASIA now provides that the FDA "shall accept data" from foreign studies if "such data are adequate under applicable standards to support approval ... or clearance" of the device.[34] Thus, while Congress may have intended to expand and standardize the circumstances under which foreign trials can support device (and drug) applications, it is unclear whether Congress meant to abrogate the regulation that disallows the use of studies that do not adequately protect human subjects. More generally, through the FDASIA Congress took numerous steps to harmonize United States and foreign regulations. For all medical products—drugs and biological products as well as devices—the FDA is directed to work with its foreign counterparts to develop "uniform, scientifically driven clinical trial standards."[35] The goal here is to speed product development, make better use of international data, and reduce duplicative studies.[36]

Congress also gave the FDA increased authority to enter into "arrangements" with foreign nations in order to harmonize device regulations, including regulations pertaining to inspections and labeling symbols.[37] And to promote this harmonization, Congress has also specifically encouraged the FDA to increase its participation in the International Medical Device Regulators Forum and other appropriate international fora.[38]

APPLICATIONS AND APPROVALS

The FDASIA amends several provisions governing applications generally and the approval process specifically. In addition, as part of the FDA's commitment to improving its processes, the FDA has provided some complimentary guidance.

Pre-Submission Meetings and Agency Guidance. Before filing substantive applications, many manufacturers and sponsors affirmatively seek guidance from the FDA. The two most commonly used pathways for obtaining such guidance, i.e., the "Pre-IDE Program" and the "Determination Meeting," have also been amended recently.

The Pre-IDE Program is often used to assess the FDA's reaction to proposed protocols for clinical trials. This program is similarly used by those preparing 510(k) submissions, PMAs, and humanitarian device exception submissions ("HDEs"). In July, the FDA renamed this program the "Pre-Submission" or "Pre-Sub" Program and issued a draft guidance document detailing the program's operation.[39] The FDA's draft sets forth in detail the type of information that should be provided in a "Pre-Sub Package," what kinds of meetings the FDA will hold, how to request a meeting, how the FDA will respond to such requests, and other relevant information. According to the FDA, this newly named program, while "entirely voluntary," is "strongly encouraged." And although the FDA does not commit to making final decisions that reflect its early feedback, the FDA intends to remain consistent with it and hopes that "careful consideration of FDA's feedback may improve the quality of subsequent submissions and facilitate the development process for new devices."

A determination meeting is a forum, provided by statute, for obtaining guidance from the FDA before filing a PMA.[40] Upon request, the FDA must meet "to determine the type of valid scientific evidence ... that will be necessary to demonstrate for purposes of approval ... the effectiveness of a device."[41] The FDA would thereafter specify in writing the data that "are necessary to establish device effectiveness."[42] Now, the FDASIA defines the term "necessary" as used in this clause to mean "the minimum required information that would support a determination ... that an application provides reasonable assurance of the effectiveness of the device."[43] This new specification is apparently designed to prevent the FDA from demanding excessive testing.

Classification, Reclassification, and Substantial Equivalence. The FDASIA also provides for adjustments to the FDA's classification system. Previously, sponsors of a novel device could not immediately ask the FDA to classify the device as a Class I or Class II device. The sponsor had to first file a 510(k) report and could not proceed to classification until the FDA determined whether or not the device was substantially equivalent to an existing device. Now, the FDASIA streamlines this practice through a new "*de novo* application process" allowing the sponsor to bypass the 510(k) submission and immediately seek appropriate classification if the sponsor believes that a device is not substantially equivalent to an existing product, and if the device is of "low-moderate risk."[44] The FDA must rule on a classification request within 120 days.[45]

The classification of a device is also subject to amending, or reclassification, when the FDA receives new information.[46] The FDASIA now amends the reclassification process by directing the FDA to proceed by administrative order, rather than by regulation.[47] The FDASIA details the notices that must be published in the Federal Register in order to promulgate such an order.[48] In the same way, the FDA must proceed by administrative order, rather than by regulation, when its seeks to regulate devices that predate the 1976 Medical Device Amendments.[49]

Substantial equivalency determinations have also been tightened by the FDASIA. The FDA may request any information that is "necessary to making substantial equivalence determinations."[50] The FDASIA now defines "necessary" to effectively limit the FDA to "the minimum required information that would support a determination of substantial equivalence."[51]

Acceptance and Filing of PMAs and 510(k)s. New FDA guidance clarifies the application and approval process. Before the FDA can approve a PMA application, it of course must first "accept" and "file" the application. In keeping with its Commitment Letter, the FDA issued a draft guidance document detailing FDA policy on acceptance and filing reviews. Importantly, this guidance document provides detailed checklists that the FDA will use when conducting these reviews.[52] In summary, the FDA will "accept" a PMA when it is "administratively complete," i.e., the application contains some information responsive to every required element. A submission will be considered "accepted" if not rejected in writing within 15 days of receipt.

Once the application is accepted, it will then proceed to an FDA filing review, "to determine the basic adequacy of the technical elements of the PMA."[53] In other words, the FDA will review the data to determine whether the data were collected in conformity with the clinical protocol, whether the data were collected on the final design of the device, whether the patient population in the clinical studies fits the device's proposed indications, and other similar and relevant issues. It is noteworthy that neither the acceptance decision nor the filing decision will be based on a substantive review of the submitted studies. A filing review should be completed within 45 days of receipt of the application.

The FDA also issued a draft guidance document with regard to its policies and checklists for a 510(k) submission.[54] As with a PMA, the FDA must "accept" a 510(k) submission before the FDA will conduct a substantive review. An "acceptance review" in the 510(k) context will assess "whether a submission is administratively complete, in that it includes all of the information necessary for the FDA to conduct a substantive review and to reach a determination regarding substantial equivalence…."[55] The FDA has committed to completing acceptance reviews within 15 calendar days of receiving the 510(k) notification.

Electronic Format of Submissions. From an administrative perspective, the most significant change relates to the format of submissions in general. Currently, applications and supplements are submitted in electronic format through the FDA eSubmitter tool only on a voluntary or optional basis. This voluntary option will soon be superseded by a mandatory electronic filing requirement. This mandate will become effective after the FDA issues its implementing guidance document.[56]

Documentation and Review of Significant Decisions. When the FDA denies a PMA or disapproves an IDE, the FDA is required to provide a written explanation.[57] Congress expanded this obligation in the FDASIA, requiring the FDA to provide "a substantive summary of the scientific and regulatory rationale for any significant decision" regarding a PMA or an IDE.[58] Also, this duty to provide a rationale extends to significant decisions regarding 510(k) reports.[59] While the phrase "significant decision" is not defined, it includes resolution of "significant controversies [and] differences of opinion."[60]

Congress also expanded the standing requirements necessary to appeal or challenge a "significant decision." *Any person*—not just an applicant—can request a "supervisory review" of a "significant decision."[61] Such a request must be submitted within 30 days of the decision. The FDA has 30 days thereafter within which to schedule an in-person or telephonic review. The FDA must finally resolve the challenge within 45 days.[62]

Consideration of Patients' Points of Views. As part of the decision-making process, the FDASIA instructs the FDA to "consider the perspectives of patients during regulatory

discussions" by identifying "patient representatives," and by inviting them to participate "in appropriate agency meetings with medical product sponsors and investigators."[63]

Pediatric Patients—Submission of Information and Demonstration Projects. Pediatric patients play an increasingly substantial role in the PMA process. The 2007 Food and Drug Administration Amendments Act originally called upon sponsors of PMAs to provide a description of the pediatric subpopulations suffering from the condition that the device is intended to treat, and an estimate of the number of affected pediatric patients.[64] Along these same lines, the FDASIA authorizes appropriations to promote pediatric device development[65] and instructs the FDA to issue implementing rules to ensure that pediatric needs are appropriately incorporated into reviews. Proposed rules on this point are due on December 31 of this year, and the final rules are due in December 2013.[66]

POST-APPROVAL STUDIES, MODIFICATIONS, AND RELATED FDA GUIDANCE DOCUMENTS

Post-Approval Studies. There are a couple of post-approval points that are worthy of mention here. First, for devices that require a PMA, the FDA may also impose a range of post-approval obligations on the manufacturer as a condition of approval.[67] Often, these obligations include time-consuming and costly de novo clinical trials. To address these inconsistencies, beginning on August 30, 2012, the FDA held a series of workshops on post-approval studies, designed to identify more efficient and faster alternatives to *de novo* clinical trials. The result: FDA participants signaled a willingness to permit manufacturers to replace these trials with studies based upon registry data, case control studies, and statistical methods to combine information from different sources. The FDA also encouraged manufacturers to "nest IDE studies into post-approval studies"—that is, to devise post-approval studies that could also serve as pivotal studies for new indications or as the control group of pivotal studies for the next generation of devices.

Post-Approval Modifications and Guidance. Second, and with regard to modifications made after a product is cleared, product innovation presents a recurring regulatory issue for manufacturers. For example, for each modification of a Class II device, the manufacturer must decide whether it needs to file another 510(k) submission. The driver of this decision is whether or not the modification is "significant," i.e., could it "significantly affect the safety or effectiveness of the device" or result in a "major change or modification in the intended use of the device."[68] Determining when a change is "major" or "significant" has proven controversial in the past, and Congress has now rejected the FDA's most recent guidance on the subject.

For many years, the FDA's interpretation of the "significant modification" rule was contained in a lengthy 1997 guidance document,[69] built around a series of flowcharts, which was supposed to help manufacturers decide whether a filing was necessary. In 2011, the FDA issued a new draft guidance document, intending to update and supersede the 1997 version.[70] In that draft, the FDA eliminated the flowcharts and attempted to provide a greater clarity, which it deemed "critical to facilitating advancements in device technology."[71] Both formally and informally,[72] the FDA stressed that the modification regulation required new submissions whenever a change *could* significantly affect functioning, and not just when the change *does* have such an effect. Congress disagreed.

The Committee Report accompanying the FDASIA expressed the view that the new FDA guidance document was even less clear than the one it replaced.[73] Congress directed the FDA to withdraw the 2011 document and reinstate the 1997 version, which is now binding upon the FDA.[74] Congress further instructed the FDA that it could not issue a new draft guidance document without first reporting to Congress about what a new guidance document on the subject might say—and then waiting for a year.[75] Until this process plays out, the FDA must follow its 1997 guidance, flowcharts and all.

CONCLUSION

Many of the new policies are designed to make the FDA's processes more efficient. Time will tell whether these good intentions result in significant improvements.

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ENDNOTES

1 FDASIA was enacted as Public Law 112-144 (126 Stat. 993). President Obama signed it on July 9, 2012.
2 FDASIA, § 207.
3 FD&C Act § 738(h)(1).
4 77 F.R. 45360 (July 31, 2012).
5 76 F.R. 45826 (August 1, 2011).
6 FDASIA, § 203(b).
7 FDASIA, § 203(b) (base fees).
8 FD&C Act, § 738(d), (e).
9 FD&C Act, § 738(a)(2)(B).
10 FDASIA, § 203(d).
11 FDA, *MDUFA Performance Goals and Procedures* (April 18, 2012) at 16.
12 76 F.R. 45826 (August 1, 2011).
13 FDASIA, § 203(b).
14 FDASIA, § 203(d).
15 77 F.R. 45927 (August 2, 2012) (promulgating new §807.20(a)(2).
16 FDASIA, § 202(3).
17 FD&C Act, § 510(i)(1).
18 FD&C Act, § 502(o).
19 FDASIA, § 702(a).
20 77 F.R. 45927 (August 2, 2012) (amending 21 C.F.R. part 807).
21 *See id.*
22 The letter is posted to the FDA web site.
23 FDASIA, § 204(b). The commitment letter (at pp. 13-15) details the information that the FDA will provide in each progress report.
24 FD&C Act, § 520(g)(4)(B).
25 FDASIA, § 601.
26 FD&C Act § 520(g)(2)(B)(ii).
27 FDASIA, §601.
28 FDASIA, § 606.
29 *See* FD&C Act, § 505(i)(3).
30 FD&C Act, § 520(g)(5).
31 FDASIA, § 606.
32 21 C.F.R. § 814.15(a), (b).
33 21 C.F.R. § 814.15(b).
34 FDASIA, § 1123.
35 FDASIA, § 1123.
36 *Id.*
37 FDASIA, § 609.
38 FDASIA, § 610.
39 FDA, *Draft Guidance for Industry and FDA Staff: Medical Devices: The Pre-Submission Program and Meetings with FDA Staff* (July 13, 2012).
40 One can also ask for a determination meeting before filing an IDE. FD&C Act, § 520(g)(7). The provision relating to IDE determination meetings was not amended by FDASIA.
41 FD&C Act, § 513(a)(3)(D)(i).
42 FD&C Act, §§ 513(a)(3)(D)(i)(ii).
43 FDASIA, § 602(a).
44 FDASIA, § 607.
45 *Id.*
46 FD&C Act, § 513(e)(1).
47 FDASIA, § 608(a).
48 *Id.*
49 FDASIA, § 608(b).
50 FD&C Act, §513(i)(1(D).
51 FDASIA, §602(b).
52 FDA, *Draft Guidance for Industry and Food and Drug Administration Staff: Acceptance and Filing Review for Premarket Approval Applications (PMAs)* (July 31, 2012).
53 *Id.*
54 FDA, *Draft Guidance for Industry and Food and Drug Administration Staff: Refuse to Accept Policy for 510(k)s* (August 13, 2012).
55 *Id.* at p. 5.
56 FDASIA, §1136.
57 FD&C Act, §§ 515(d)(1)(A)(ii), 520(g)(4)(B).
58 FDASIA, § 603.
59 *Id.*
60 *Id.*
61 FDASIA, § 603.
62 *Id.*
63 FDASIA, § 1137.
64 FD&C Act, § 515A(a).
65 FDASIA, § 620(a).
66 FDASIA, § 620(b).
67 21 C.F.R. § 814.82.
68 21 C.F.R. § 807.81(a)(3).
69 FDA, *Deciding When to Submit a 510(k) for a Change to an Existing Device* (January 10, 1997).
70 FDA, *Guidance for Industry and FDA Staff: 510(k) Device Modifications: Deciding When to Submit a 510(k) for a Change to an Existing Device* (July 27, 2011).
71 *Id.* at 2.
72 *See* Foreman, Christy (Dir. of ODE), *510(k) Device Modifications: Deciding When to Submit a 510(k) for a Change to an Existing Device.*
73 *See* House Report 112-495 at 27-28 (May 25, 2012).
74 FDASIA, § 604.
75 *Id.*