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Access to Clinical Devices through Nontraditional Routes

Robert J. Klepinski



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ROBERT J. KLEPINSKI*

I. INTRODUCTION

While clinical devices are normally provided to trial subjects under traditional protocols and Investigational Device Exemption (IDE) rules,¹ there are many situations where there is a pressing need to use other methods to make the device available before commercial release. Congress and the United States Food and Drug Administration (FDA) have established various regulatory pathways to address this need.

This article is a synopsis of the various possible methods and their relative practicality. The difficult question for industry is what rules apply to these uses and what compliance positions may be taken by FDA.

The following regulatory pathways will be addressed:

- Emergency Use
- Compassionate Use
- Continued Access
- Treatment IDE

This article also discusses the relevance of Custom Devices, which are separately described in detail in a previous article by this author.²

Each of these pathways has different origins, different requirements and different degrees of usefulness. Some grow out of a statutory basis while some are creatures of guidance. The source of each and its practical uses will be discussed.

II. EMERGENCY USE

Emergency use has been allowed under long-standing FDA policy. It has been incorporated into the Food, Drug, and Cosmetic Act (FDCA)³ by the Food and Drug Administration Modernization Act (FDAMA) in 1997.⁴ An emergency use was originally defined by FDA as one that requires the use of an unapproved device to save the life of a patient, outside the normal protocol of an IDE. FDA's older guidance stated:

Each of the following conditions should exist for a situation to be considered an emergency:

* Mr. Klepinski is an officer of Fredrikson & Byron, P.A., in Minneapolis, MN. He was formerly the regulatory attorney for Medtronic, Inc.

¹ 21 C.F.R. pt. 812.

² See Robert J. Klepinski, *Old Customs, Ancient Lore: The Development of Custom Device Law Through Neglect*, 61 *FOOD DRUG L.J.* 237-249 (2006).

³ Federal Food, Drug, and Cosmetic Act, June 25, 1938, ch. 675, 52 Stat. 1040 (21 U.S.C. §§ 301 et seq.).

⁴ Food and Drug Administration Modernization Act, Pub. L. 105-115, Nov. 21, 1997, 111 Stat. 2296 (as added, title IV, § 402, 111 Stat. 2365); (21 U.S.C. § 360bbb (FDCA § 561)).

- the patient is in a life threatening condition that needs immediate treatment;
- no generally acceptable alternative for treating the patient is available; and
- because of the immediate need to use the device, there is no time to use existing procedures to get FDA approval for the use.⁵

FDAMA statutorily blessed this process by adding the following to the FDCA at Section 561:

The Secretary may, under appropriate conditions determined by the Secretary, authorize the shipment of investigational drugs or investigational devices for the diagnosis, monitoring, or treatment of a serious disease or condition in emergency situations.⁶

Note that Section 561 neither demanded nor suggested FDA regulation, and FDA has never promulgated a specific regulation for emergency uses. Its regulation has been under the process for IDE protocol deviations, which resides in two locations in the IDE regulation.⁷ First, the actions of the prescribing physician are found in the regulation on investigator reports:

Deviations from the investigational plan. An investigator shall notify the sponsor and the reviewing IRB (see Sec. 56.108(a) (3) and (4)) of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred.⁸

Sponsor obligations on emergency uses are found in the regulations on IDE supplements:

Changes effected for emergency use. The requirements of paragraph (a)(1) of this section regarding FDA approval of a supplement do not apply in the case of a deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such deviation shall be reported to FDA within 5-working days after the sponsor learns of it (see Sec. 812.150(a)(4)).⁹

Note that the standard “protect the life or physical well-being of a subject in an emergency” is different from the traditional FDA standard of “save the life” or “life-threatening.” Is “physical well-being” a broader standard? Where did this come from? The FDCA language¹⁰ contained no standard but allowed the FDA to promulgate the regulation.

⁵ Center for Devices and Radiological Health (CDRH), FDA, Guidance For Emergency Use Of Unapproved Medical Devices (Oct. 22, 1985), available at www.fda.gov/cdrh/manual/unappr.html (hereinafter “Emergency Use Guidance”).

⁶ FDCA § 561(a) (21 U.S.C. 360bbb).

⁷ 812, *supra*.

⁸ 21 C.F.R. 812.150(A)(4).

⁹ *Id.* § 812.35(a)(2).

¹⁰ FDCA § 561, *supra*.

The later guidance on IDE policies¹¹ includes a discussion of emergency use. It cites the regulatory standard but then goes on to parallel the former guidance.¹² Therefore, there is nowhere an explanation of the term “physical well-being.” It appears that FDA uses the more stringent “life-threatening” or “life-saving” standard, and not the “physical well-being” standard.

These emergency cases may arise virtually anywhere. It could be at a hospital which was not an investigational site under an IDE. It could be at an investigational site but the patient might be outside the enrollment criteria for the study. In a more unusual situation, it might even be before the IDE is approved.

In spite of these minor inconsistencies, emergency use is the most clearly delineated of the nontraditional access routes, in statute, regulation, and guidance.

III. COMPASSIONATE USE

Compassionate use is meant for patient needs similar to those of emergency use but requires prior FDA approval. The process is described in guidance on the FDA web site:

The compassionate use provision allows access for patients who do not meet the requirements for inclusion in the clinical investigation but for whom the treating physician believes the device may provide a benefit in treating and/or diagnosing their disease or condition. This provision is typically approved for individual patients but may be approved to treat a small group.¹³

The guidance establishes criteria for this type of use:

Criteria:

- Serious disease or condition
- No alternative

Time-frame: During clinical trial

FDA recognizes that there are circumstances in which an investigational device is the only option available for a patient faced with a serious, albeit not life-threatening, disease or condition. In these circumstances, FDA uses its regulatory discretion in determining whether such use of an investigational device should occur.¹⁴

One major distinction from emergency use is the need, under FDA guidance, to obtain prior approval:

Prior FDA approval is needed before compassionate use occurs. In order to obtain Agency approval, the sponsor should submit an IDE supplement requesting approval for a protocol deviation under section § 812.35(a) in order to treat the patient. The IDE supplement should include:

¹¹ Center for Devices and Radiological Health (CDRH), FDA, Guidance on IDE Policies and Procedures (Jan. 20, 1998) available at: <http://www.fda.gov/cdrh/ode/idepolicy.html> (hereinafter “IDE Guidance”).

¹² Emergency Use Guidance, *supra*.

¹³ Center for Devices and Radiological Health (CDRH), FDA, Device Advice-Early Expanded Access, available at: <http://www.fda.gov/cdrh/devadvice/ide/early.shtml> (hereinafter “Device Advice”).

¹⁴ Device Advice, *supra*.

1. A description of the patient's condition and the circumstances necessitating treatment;
2. A discussion of why alternative therapies are unsatisfactory and why the probable risk of using the investigational device is no greater than the probable risk from the disease or condition;
3. An identification of any deviations in the approved clinical protocol that may be needed in order to treat the patient; and
4. The patient protection measures that will be followed. (Informed consent, concurrence of IRB chairperson, clearance from the institution, independent assessment from uninvolved physician, authorization from IDE sponsor)

The physician should not treat the patient identified in the supplement until FDA approves use of the device under the proposed circumstances. In reviewing this type of request, FDA will consider the above information as well as whether the preliminary evidence of safety and effectiveness justifies such use and whether such use would interfere with the conduct of a clinical trial to support marketing approval.¹⁵

While there are no regulations for this process, FDA attempts, in guidance, to create a semblance of structure:

If the request is approved, the attending physician should devise an appropriate schedule for monitoring the patient, taking into consideration the investigational nature of the device and the specific needs of the patient. The patient should be monitored to detect any possible problems arising from the use of the device. Following the compassionate use of the device, a follow-up report should be submitted to FDA as an IDE supplement in which summary information regarding patient outcome is presented. If any problems occurred as a result of device use, these should be discussed in the supplement and reported to the reviewing IRB as soon as possible.

The above compassionate use criteria and procedures can also be applied when a physician wishes to treat a few patients rather than an individual patient suffering from a serious disease or condition for which no alternative therapy adequately meets their medical need. In this case, the physician should request access to the investigational device through the IDE sponsor. The sponsor should submit an IDE supplement that includes the information identified above and indicates the number of patients to be treated. Such a supplement should include the protocol to be followed or identify deviations from the approved clinical protocol. As with single patient compassionate use, a monitoring schedule should be designed to meet the needs of the patients while recognizing the investigational nature of the device. Follow-up information on the use of the device should be submitted in an IDE supplement after all compassionate use patients have been treated.¹⁶

¹⁵ Device Advice, *supra*.

¹⁶ Device Advice, *supra*.

This on-line guidance uses the standard of “serious disease” which is taken from the following FDCA section created by FDAMA:

(b) **INDIVIDUAL PATIENT ACCESS TO INVESTIGATIONAL PRODUCTS INTENDED FOR SERIOUS DISEASES.**—Any person, acting through a physician licensed in accordance with State law, may request from a manufacturer or distributor, and any manufacturer or distributor may, after complying with the provisions of this subsection, provide to such physician an investigational drug or investigational device for the diagnosis, monitoring or treatment of a serious disease or condition if—

- 1) the licensed physician determines that the person has no comparable or satisfactory alternative therapy available to diagnose, monitor or treat the disease or condition involved, and that the probable risk to the person from the investigational drug or investigational device is not greater than the probable risk from the disease or condition;
- 2) the Secretary determines that there is sufficient evidence of safety and effectiveness to support the use of the investigational drug or investigational device in the case described in paragraph (1);
- 3) the Secretary determines that provision of the investigational drug or investigational device will not interfere with the initiation, conduct or completion of clinical investigations to support marketing approval; and
- 4) the sponsor, or clinical investigator, of the investigational drug or investigational device submits to the Secretary a clinical protocol consistent with the provisions of section 505(i) or 520(g), including any regulations promulgated under section 505(i) or 520(g), describing the use of the investigational drug or investigational device in a single patient or a small group of patients.¹⁷

No regulations have been promulgated to implement Section 561(b). FDA handles these requests as IDE supplements.¹⁸

FDA expects that steps will be taken to protect patient rights and safety:

In the event that a device is used in circumstances meeting the criteria listed above, FDA would expect the physician to follow as many patient protection procedures as possible. These include obtaining:

- an independent assessment by an uninvolved physician;
- informed consent from the patient or a legal representative;
- institutional clearance as specified by institutional policies;
- the IRB chairperson’s concurrence; and
- authorization from the sponsor, if an approved IDE for the device exists.¹⁹

The standard of patient health is lower than an emergency use. The disease state need only be “serious.” There must be, however, the decision by FDA that the ben-

¹⁷ FDCA § 561 (21 U.S.C. 360bbb).

¹⁸ 21 C.F.R. 812.35(a).

¹⁹ Emergency Use Guidance, *supra*.

efits outweigh any risk. In effect, the Office of Device Evaluation (ODE) personnel are making one-by-one treatment calls on individual patient cases.

The division between emergency use and compassionate use is not always clear with regard to timing. For example, how does one determine if there is sufficient time to obtain FDA approval in order to classify a use as compassionate? What if the patient requires treatment in a time shorter than the 30 days FDA has to respond to an IDE supplement?²⁰ There is no FDA guidance on what the dividing line is. This will be discussed in more detail below along with other compliance issues.

IV. CONTINUED ACCESS

Continued access is the process under which a clinical study is continued after the original enrollment limit has been reached in order to serve a public health need. Consider a case where a new technology is the subject of an IDE study. After the necessary data is gathered and a Premarket Approval Application (PMA) is submitted, there will naturally be a time before approval where this technology will not normally continue to be available to patients. FDA has traditionally allowed expansion of the clinical enrollment numbers and, perhaps, sites in order to serve a patient population that would otherwise not have access to the devices. This was especially important in past decades when review times for PMAs were extending well beyond the statutory time limits.

This informal practice was recorded in a Blue Book Memorandum stating:

ODE has traditionally permitted sponsors of clinical investigations to continue to enroll subjects at a pre-determined rate while a marketing application is being prepared by the sponsor or reviewed by the Office if there is: 1) a public health need for the device or 2) if there is preliminary evidence that the device is likely to be effective and no significant safety concerns have been identified for the proposed indication. Such a policy is scientifically sound as it allows the sponsors to collect additional safety and effectiveness data in support of the marketing application or to address new questions regarding the investigational device during this intervening period. This approach is also administratively appropriate as the preparation and review times for a marketing application can be lengthy; and thus, it could be contrary to the public health to prevent access to these potentially safe and effective new devices during a lengthy evaluation period.²¹

Once again, since the method is not embodied in regulation, the Blue Book Memorandum attempts to provide some process:

Once a preliminary review of the data (IDE, 510(k), or PMA) indicates that there is evidence of safety and effectiveness, a sponsor may propose to conduct an "extended" clinical investigation of the device. An extended investigation may be conducted for a number of reasons. For example, a sponsor may propose an extended trial for the same indication for use as studied under the IDE and use the same study protocol to provide confir-

²⁰ 21 C.F.R. 812.30(a)(1).

²¹ Center for Devices and Radiologic Health (CDRH), FDA, Guidance: Continued Access to Investigational Devices During PMA Preparation and Review, Blue Book Memorandum D96-1, (July 15, 1996), available at: <http://www.fda.gov/cdrh/d961.html> (hereinafter "Continued Access Guidance").

matory evidence of safety and effectiveness. A modified clinical protocol may be used to better define safety and effectiveness in a subpopulation, to support new indications for use or new modalities of use for the device, to identify and quantify adverse reactions, to address long-term effects of the device, to support additional labeling claims or to confirm that minor changes made to the device design or to the conditions under which the device will ultimately be used do not substantially impact safety and effectiveness.²²

As in Compassionate Uses, the IDE supplement is used as the all-purpose tool for implementing this mode of access:

A request for an extended investigation must be submitted by the sponsor of the IDE in writing as a supplement to the IDE. When reviewing a request for an extended investigation from the sponsor, the sponsor's justification for the extension, the preliminary safety and effectiveness data (IDE, 510(k) or PMA), the risks posed by the device, the proposed rate of continued enrollment, the proposed objectives for the extended study, the sponsor's progress toward submission of the marketing application and/or ODE's progress in the review of the marketing application should be considered. All of these factors may influence ODE's decision to approve, approve with modifications or disapprove the proposed protocol for this intervening period between completion of the core clinical investigation and approval of the marketing application. The above factors should also be considered by ODE when deciding upon an appropriate rate of enrollment, number of investigators and number of investigational sites for the study during this stage of product development. Finally, a sponsor who has been negligent in his monitoring responsibilities or who has exhibited other unresolved compliance problems would not be permitted to participate in an extended investigation.²³

Unlike Compassionate Use, these devices are usually under an existing protocol and are well described in an IDE application. Therefore, conduct of the Continued Access will be under normal IDE regulations:

An investigation conducted under the provisions of this policy must still be conducted in accordance with the IDE, IRB, and Informed Consent regulations (21 CFR 812, 56 and 50, respectively). FDA may withdraw approval for the extended investigation for any of the reasons identified in 21 CFR 812.30 (b), if the device is being commercialized, or if there is not satisfactory progression towards submission of the marketing application or towards approval of the marketing application. As in the withdrawal of approval of an IDE, however, ODE must make every attempt to resolve the issue(s) with the sponsor, must notify the sponsor in writing of the issue(s), and must notify the IDE Staff and the Director's office before proceeding with this course of action.²⁴

²² Continued Access Guidance, *supra*.

²³ Continued Access Guidance, *supra*.

²⁴ Continued Access Guidance, *supra*.

FDA acted, apparently driven by public policy issues, without Congressional mandate or promulgation of regulations.

While there is some overlap with treatment use, continued access allows a relatively simple path toward patient access, using standard clinical practices. The process of continued access is well-defined by policy and tradition, although it is not addressed in the statute or regulations. The sponsor of a clinical investigation is permitted to continue to enroll subjects while a marketing application is being prepared by the sponsor and/or reviewed by the Agency. The criteria are i) a public health need for the device, or ii) preliminary evidence that the device is likely to be effective and no significant safety concerns have been identified for the proposed indication. The process is defined on the FDA web site as follows:

FDA may allow continued enrollment of subjects after the controlled clinical trial under an IDE has been completed in order to allow access to the investigational medical device while the marketing application is being prepared by the sponsor or reviewed by FDA.

Criteria:

- Public health need or
- Preliminary evidence that the device will be effective and there are no significant safety concerns

Time-frame: After completion of the clinical trial

The sponsor of a clinical investigation is permitted to continue to enroll subjects while a marketing application is being prepared by the sponsor and/or reviewed by the agency if there is:

- A public health need for the device; or
- Preliminary evidence that the device is likely to be effective and no significant safety concerns have been identified for the proposed indication.²⁵

The web site sets out the process as:

The continued enrollment of subjects in an investigation while a marketing application is being prepared by the sponsor and/or reviewed by ODE is known as an "extended investigation." Extended investigations permit patients and/or physicians continued access to the devices while also allowing the collection of additional safety and effectiveness data to support the marketing application or to address new questions regarding the investigational device. The Continued Access Policy may be applied to any clinical investigation that meets the criteria identified above; however, it is intended to be applied late in the device development process, i.e., after the controlled clinical trial has been completed.

A sponsor's request for an extended investigation should be submitted as an IDE supplement and include the following information:

1. A justification for the extension;
2. A summary of the preliminary safety and effectiveness data generated under the IDE;

²⁵ Device Advice, *supra*.

3. A brief discussion of the risks posed by the device;
4. The proposed rate of continued enrollment (the number of sites and subjects);
5. The clinical protocol, if different from that used for the controlled clinical trial, as well as the proposed objectives for the extended study; and
6. A brief discussion of the sponsor's progress in obtaining marketing approval/clearance for the device.²⁶

This established route to provide devices during PMA review has been successfully and often used, according to anecdotal reports. As IDE data is confidential, FDA does not publish reports on the frequency with which this occurs.

V. TREATMENT IDE

This alone, of the various access methods, is fully specified in statute and regulation. FDAMA added this section to the FDCA to allow for early access to devices that treat immediately life-threatening diseases:

(c) TREATMENT INVESTIGATIONAL NEW DRUG APPLICATIONS AND TREATMENT INVESTIGATIONAL DEVICE EXEMPTIONS.—Upon submission by a sponsor or a physician of a protocol intended to provide widespread access to an investigational drug or investigational device for eligible patients (referred to in this subsection as an “expanded access protocol”), the Secretary shall permit such investigational drug or investigational device to be made available for expanded access under a treatment investigational new drug application or treatment investigational device exemption if the Secretary determines that—

- 1) under the treatment investigational new drug application or treatment investigational device exemption, the investigational drug or investigational device is intended for use in the diagnosis, monitoring or treatment of a serious or immediately life-threatening disease or condition;
- 2) there is no comparable or satisfactory alternative therapy available to diagnose, monitor or treat that stage of disease or condition in the population of patients to which the investigational drug or investigational device is intended to be administered;
- 3)A) the investigational drug or investigational device is under investigation in a controlled clinical trial for the use described in paragraph 1) under an investigational drug application in effect under section 505(i) or investigational device exemption in effect under section 520(g); or
B) all clinical trials necessary for approval of that use of the investigational drug or investigational device have been completed;
- 4) the sponsor of the controlled clinical trials is actively pursuing marketing approval of the investigational drug or investigational device for the use described in paragraph 1) with due diligence;

²⁶ Device Advice, *supra*.

5) in the case of an investigational drug or investigational device described in paragraph 3)A), the provision of the investigational drug or investigational device will not interfere with the enrollment of patients in ongoing clinical investigations under section 505(i) or 520(g);

6) in the case of serious diseases, there is sufficient evidence of safety and effectiveness to support the use described in paragraph 1); and

7) in the case of immediately life-threatening diseases, the available scientific evidence, taken as a whole, provides a reasonable basis to conclude that the investigational drug or investigational device may be effective for its intended use and would not expose patients to an unreasonable and significant risk of illness or injury.

A protocol submitted under this subsection shall be subject to the provisions of section 505(i) or 520(g), including regulations promulgated under section 505(i) or 520(g). The Secretary may inform national, State, and local medical associations and societies, voluntary health associations, and other appropriate persons about the availability of an investigational drug or investigational device under expanded access protocols submitted under this subsection. The information provided by the Secretary, in accordance with the preceding sentence, shall be the same type of information that is required by section 402(j)(3) of the Public Health Service Act.²⁷

The regulations promulgated by FDA²⁸ define “immediately life-threatening” as “a stage of a disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment.”

FDA included diagnostic devices in this definition.

This standard is more severe than any of the other early access methods. On the other hand, treatment use is available to a larger potential patient base at an earlier time in the clinical trial than continued access.

It is not clear exactly what parts of this statute and regulation have made it unpopular, but it is clear that it has not achieved Congress’ desire to make devices available. This author knows of no implementation of treatment use. Once again, these IDEs would be confidential and FDA displays no public records of treatment uses. However, there have never even been anecdotal reports of such IDEs being done. When asked at conferences, FDA personnel who would be in a position to know were unaware of any.

It appears that this alternative has been unattractive to sponsors of device clinical trials.

VI. COMPARISON OF EARLY ACCESS PATHWAYS

The various pathways may be compared by examining the similarities and differences in the patients that may be treated, the timeframes and the need for FDA interaction.

What type of patient is to be treated?

²⁷ FDCA § 561 (21 U.S.C. 360bbb).

²⁸ 21 C.F.R. 812.36.

1. Emergency Use – life-threatening condition that needs immediate treatment.
2. Compassionate Use – patient with serious, not necessarily life-threatening disease for whom the treating physician believes the device may provide a benefit in treating and/or diagnosing their disease or condition.
3. Continued Access – same patients as existing IDE unless there is other protocol approved by FDA.
4. Treatment Use – serious or immediately life-threatening disease or condition with reasonable likelihood of death.

What time frame is available?

1. Emergency Use – before and during an IDE study.
2. Compassionate Use – before and during an IDE study.
3. Treatment Use – after an IDE study starts and up to market approval.
4. Continued Access – during an IDE study and up to market approval, usually after the main study is complete.

What FDA approval or notification is needed?

1. Emergency Use – no approval, notice to sponsor within 5 days, notice to FDA within 5 days.
2. Compassionate Use – IDE supplement approved by FDA.
3. Continued Access – IDE supplement approved by FDA.
4. Treatment Use – treatment IDE approved by FDA.

VII. COMPLIANCE ISSUES

There are no special compliance issues associated with continued access or treatment use. In the case of continued access, it is because compliance involves the same regulations²⁹ as the usual part of the clinical trial. In the case of treatment use, it is because there is a dearth of activity in the area, hence no issues.

For emergency use and compassionate use, however, there are countless possibilities for compliance issues. These arise for a variety of reasons, both regulatory and practical.

A. *Timing Issues*

As discussed above, the boundary between what constitutes emergency use and compassionate use is unclear. An emergency use is one in which there is not enough time to get FDA pre-approval. However, how much time is enough? There is no guidance on this topic.

In one instance, a device company received its approval for compassionate use approximately 30 days after submission, showing that FDA was using its full regulatory time period for review of an IDE supplement. The company then viewed 30 days as the boundary between emergency use and compassionate use. Then, when the reviewing division in ODE learned of the emergency use, they said it was non-compliant. The reviewer suggested that compassionate use be faxed in, with email notice, and that they would be expedited, in as little as three days. Then the reviewer changed. When the company next submitted a compassionate use, it took

²⁹ 21 C.F.R. 812.

four days, which was too late for this particular patient. The reviewer indicated they could not clear the paper work in that time.

So what is the time difference between the two pathways? How is a doctor or a sponsor of an IDE to know what is an emergency? It is clearly something less than 30 days. A compassionate use is clearly over three or four days. But how to tell? Only by close contact with a reviewing division and negotiation on a review-by-reviewer basis can a company establish the time frame for a particular product. Based upon the absence of regulation, it is difficult to see how FDA can take compliance action based upon any particular time frame.

B. What is a Compassionate Use Device?

The FDCA and the guidance both refer to a compassionate use device as an investigational device. However, FDA has used the compassionate use pathway for devices that are not currently under IDE. For example, FDA has steered companies with what appeared to be custom devices into the compassionate use pathway. FDA appears to have an abhorrence for the FDCA Custom Device provision, usually calling custom devices “rare.” As a result, some devices that appear to fit the custom device section of the FDCA perfectly are instead channeled into this route.

One company was conducting an IDE study of a device. They had a request for a “custom-made” device by a doctor who knew of their technology. The requested device was for a different indication from the IDE, for a different patient than the IDE enrollment criteria, and for use in a different part of the body from the IDE device. Nevertheless, it was decided to call this a compassionate use. This raises the question: what is an investigational device under this statute and guidance? If the only underlying similarity to the investigational device was the underlying technology, why was it a compassionate use? What standards are to be followed in using the device if it is not described in a protocol? What standards are to be followed in analyzing adverse events?

When the compassionate use device is identical to an IDE device under study, but is used outside the protocol, at least some parts of the IDE give guidance. When the device is different from the device being studied under the IDE, compliance is a completely open issue.

C. What Controls Should a Company have on Manufacturing an Emergency Use or Compassionate Use Device?

As investigational devices, a compassionate use device or an emergency use device is exempt³⁰ from Good Manufacturing Practices (GMP), or more correctly for devices, the Quality Systems Regulation (QSR).³¹ Investigational devices are made under the conditions described in the IDE application.³² If the compassionate use device is the one that is being studied under the IDE, it will be manufactured under the IDE. If, however, the compassionate use differs from the IDE device, what controls its manufacture? It is not controlled by QSR and its manufacture is not described in the IDE.

³⁰ FDCA § 520(g)(2)(A) (21 U.S.C. 360j(g)(2)(A)).

³¹ 21 C.F.R. 820.

³² *Id.* § 812.20(b)(3).

FDA has issued at least one Warning Letter accusing a company of not manufacturing a compassionate use device under GMP/QSR. Is this a non sequitur?

D. *How is Compliance by the Doctor Achieved?*

One possibility under emergency use or compassionate use is that a health care practitioner who is not an investigator under the IDE may be using the product. In this case, there is no investigator agreement, no investigational plan and no protocol other than the use submitted by the doctor. To what standards will the sponsor be held for achieving compliance? Will FDA field personnel inspect this as a normal investigational device, expecting all the usual documentation and control?

E. *Will Adverse Events be Reported?*

If the process is not under a regulation, how will adverse events be collected or reported?

For the usual case, where an emergency use or compassionate use device is identical to a device being studied under an IDE and is being used by an investigator who is participating under the IDE, then the standard reporting rules will make sense. The investigator will report to the sponsor, who will include the events in annual progress reports, or in the case of unanticipated adverse device effects, report them promptly.

What if the device differs from the IDE device? There is no protocol defining an adverse event. Since the device is different, reporting the adverse event with the IDE results really does not make sense. It is a *sui generis* situation.

In the case where an IDE device is used by a health care practitioner who is not an investigator under the IDE study, there is no investigator agreement to define obligations as to adverse events. The use is different from the IDE use, so adverse events may be interesting but not directly relevant to the IDE product. FDA asks that the physician “monitor” the patient³³ for adverse events. There is no stated reporting expectation.

If adverse events occur and they are espied by an FDA field investigator, is there any regulatory basis for examining how they should be handled?

Uncertainty in a regulated environment is always risky for device companies. It can bring disparate opinions from various FDA personnel on what exactly is compliant. It can result in compliance actions which appear incongruous, such as the example above where the company was called noncompliant for not making an investigational device under GMP. This environment almost allows a personal control of the use by FDA, rather than the traditional regulatory control. Companies must tread lightly and try to follow the *ad hoc* wishes of whatever FDA personnel are controlling in each situation.

VIII. EFFECT ON HUMANITARIAN USE DEVICES

Humanitarian Use Devices (HUDs)³⁴ are distributed under a marketing approval known as a Humanitarian Device Exemption (HDE)³⁵ rather than an IDE. However, HUDs are limited in number and require review at each site by an Institutional

³³ IDE Guidance, *supra*.

³⁴ 21 C.F.R. 814.100 et seq.

³⁵ 21 U.S.C. 360j(m).

Review Board (IRB), giving it a hybrid look which includes some of these indicia of investigational products. As a result, FDA recognizes that there may be uses outside the scope of the HDE. FDA has issued guidance.³⁶

As a legally marketed device, one would assume that an HUD was subject to FDCA Section 906³⁷ which would allow a health care practitioner to prescribe for any disease state. However, the FDA guidance treats off-label cases as either emergency use or compassionate use.³⁸ The guidance goes on to recommend following the IDE guidance on emergency use.³⁹

With regard to compassionate use of an HUD, the guidance states:

Can a HUD be used for compassionate use if the situation is not an emergency, but a physician determines there is no alternative device for the patient's condition?

Yes, a HUD may be used for compassionate use. As in the case of emergency use, FDA recommends that the physician ensure that patient protection measures discussed above are addressed before the device is used. In addition, we recommend you first obtain FDA approval for compassionate use.⁴⁰

The guidance provides some process for using an HUD in this manner:

FDA believes that a physician who wishes to use a HDE-approved device for compassionate use should provide the HDE holder with:

- a description of the patient's condition and
- the circumstances necessitating use of the device,
- a discussion of why alternative therapies or diagnostics are unsatisfactory
- information to address the patient protection measures.

³⁶ Center for Devices and Radiological Health (CDRH), FDA, Guidance for Industry and FDA Staff - Humanitarian Device Exemption (HDE) Regulation: Questions and Answers (July 18, 2006) available at <http://www.fda.gov/cdrh/ode/guidance/1381.pdf> (hereinafter "HDE Guidance").

³⁷ Nothing in this Act shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship. This section shall not limit any existing authority of the Secretary to establish and enforce restrictions on the sale or distribution, or in the labeling, of a device that are part of a determination of substantial equivalence, established as a condition of approval or promulgated through regulations. Further, this section shall not change any existing prohibition on the promotion of unapproved uses of legally marketed devices. FDCA § 906 (21 U.S.C. 396).

³⁸ In an emergency situation, can a HUD be used off-label (i.e., outside of its approved indication for use)?

Yes. In an emergency situation, a HUD may be used off-label, but FDA recommends you follow certain patient protection measures before use. Because IRB review and approval is required before a HUD is used within its approved labeling, FDA believes similar procedures should apply if you use a HUD outside of its approved labeling. That is, in an emergency situation, a HUD may be used off-label to save the life or protect the physical well-being of a patient; however, in this situation, FDA recommends that the physician and HDE holder follow the same emergency use procedures that govern the use of unapproved devices.

HDE Guidance, *supra*.

³⁹ IDE Guidance, *supra*.

⁴⁰ HDE Guidance, *supra*.

We also recommend the HDE holder submit the above information in a HDE report for FDA approval before the use occurs to help ensure adequate patient protection. FDA will review the information in the most expeditious manner possible and issue a letter to the HDE holder.⁴¹

Once again, there is uncertainty as to compliance issues. The guidance gives an informal process for conducting such a use:

If the physician undertakes a compassionate use, he or she should devise a schedule for monitoring the patient, taking into consideration the specific needs of the patient and the limited information available regarding the risks and benefits of the device for this unapproved use. See Guidance on IDE Policies and Procedures for further discussion of the post-approval procedures for compassionate use cases, including the submission of a follow-up report to FDA.⁴²

All of this is informal, with guidance piled upon guidance. Note that the HUD guidance “recommends” following some of the procedures in the IDE guidance,⁴³ including seeking FDA approval. There is no FDA regulation under which to seek approval and there is no authority cited for this process.

Thus, the HDE guidance appears to be an aspirational goal unsupported by statute or regulation.

IX. CONCLUSION

Both Congress and FDA are sensitive to the needs of the seriously ill who might be helped by new, as yet unapproved, medical devices. FDA has long exercised policies, without specific statutory mandate and often without regulation, to satisfy this need.

Device companies should be aware of this panoply of tools for getting investigational devices to those who need them outside an IDE and the pros and cons of each. Because of the paucity of regulation and guidance for some issues, however, FDA interpretations of compliance may vary widely. It is imperative that device suppliers be aware of the compliance risks that can come from these uncertainties in the system.

⁴¹ HDE Guidance, *supra*.

⁴² HDE Guidance, *supra*.

⁴³ IDE Guidance, *supra*.