a location where the requirements of this AD can be accomplished.

(f) An alternative method of compliance or adjustment of the compliance times that provides an equivalent level of safety may be used if approved by the Manager, Small Airplane Directorate, FAA, 1201 Walnut, suite 900, Kansas City, Missouri 64106. The request shall be forwarded through an appropriate FAA Maintenance Inspector, who may add comments and then send it to the Manager, Small Airplane Directorate.

Note 2: Information concerning the existence of approved alternative methods of compliance with this AD, if any, may be obtained from the Small Airplane Directorate.

(g) Questions or technical information related to the service information referenced in this AD should be directed to Avions Pierre Robin, 1, route de Troyes, 21121 Darois-France; telephone: 33–3 80 44 20 50; facsimile: 33–3 80 35 60 80. This service information may be examined at the FAA, Central Region, Office of the Regional Counsel, Room 1558, 601 E. 12th Street, Kansas City, Missouri 64106.

Note 3: The subject of this AD is addressed in issued French AD 82–70–(A), dated May 19, 1982.

Issued in Kansas City, Missouri, on February 2, 1999.

Michael Gallagher,

Manager, Small Airplane Directorate, Aircraft Certification Service.

[FR Doc. 99–2902 Filed 2–5–99; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 876

[Docket No. 98N–1134]

Gastroenterology and Urology Devices; Reclassification of the Extracorporeal Shock Wave Lithotripter

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing for public comment its proposal to reclassify from class III to class II the extracorporeal shock wave lithotripter, when intended for use to fragment kidney and ureteral calculi, and the recommendation of the Gastroenterology and Urology Devices Advisory Panel (the Panel) regarding this reclassification. The Panel made this recommendation after reviewing the relevant publicly available information and the proposed reclassification. FDA is also issuing for public comment its tentative findings on the Panel's recommendation. After considering any public comments on the Panel's recommendation and FDA's tentative findings, FDA will reclassify the device or retain it in class III. FDA's decision on the proposed reclassification will be announced in the **Federal Register**.

DATES: Written comments by May 10, 1999.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: John H. Baxley, Center for Devices and Radiological Health (HFZ–470), Food and Drug Administration, 9200 Corporate Blvd., Rockville, MD 20850, 301–594–2194.

SUPPLEMENTARY INFORMATION:

I. Background

The Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 301 *et. seq.*), as amended by the Medical Device Amendments of 1976 (the 1976 amendments) (Pub. L. 94–295), the Safe Medical Devices Act of 1990 (the SMDA) (Pub. L. 101–629), and the Food and Drug Administration Modernization Act of 1997 (the FDAMA) (Pub. L. 105–115), established a comprehensive system for the regulation of medical devices intended for human use. Section 513 of the act (21 U.S.C. 360c) established three categories (classes) of devices, depending on the regulatory controls needed to provide reasonable assurance of their safety and effectiveness. The three categories of devices are class I (general controls), class II (special controls), and class III (premarket approval).

Under section 513 of the act, devices that were in commercial distribution before May 28, 1976 (the date of enactment of the 1976 amendments), generally referred to as preamendments devices, are classified after FDA has: (1) Received a recommendation from a device classification panel (an FDA advisory committee); (2) published the panel's recommendation for comment, along with a proposed regulation classifying the device; and (3) published a final regulation classifying the device. FDA has classified most preamendments devices under these procedures.

Devices that were not in commercial distribution prior to May 28, 1976, generally referred to as postamendments devices, are classified automatically by statute (section 513(f) of the act (21 U.S.C. 360c(f))) into class III without any FDA rulemaking process. Those devices remain in class III and require premarket approval, unless and until the device is reclassified into class I or II or FDA issues an order finding the device to be substantially equivalent, under section 513(i) of the act (21 U.S.C. 360c(i)), to a predicate device that does not require premarket approval. The agency determines whether new devices are substantially equivalent to previously offered devices by means of premarket notification procedures in section 510(k) of the act (21 U.S.C. 360(k)) and part 807 of the regulations (21 CFR part 807).

A preamendments device that has been classified into class III may be marketed, by means of premarket notification procedures, without submission of a premarket approval application (PMA) until FDA issues a final regulation under section 515(b) of the act (21 U.S.C.360e(b)) requiring premarket approval.

Reclassification of classified postamendments devices is governed by section 513(f)(2) of the act (21 U.S.C. 360c(f)(2)). This section provides that FDA may initiate the reclassification of a device classified into class III under section 513(f)(1) of the act, or the manufacturer or importer of a device may petition the Secretary of Health and Human Services (the Secretary) for the issuance of an order classifying the device in class I or class II. FDA's regulations in 21 CFR 860.134 set forth the procedures for the filing and review of a petition for reclassification of such class III devices. In order to change the classification of the device, it is necessary that the proposed new class have sufficient regulatory controls to provide reasonable assurance of the safety and effectiveness of the device for its intended use.

Section 216 of FDAMA replaced the ''four of a kind'' rule in the old section 520(h)(4) of the act (21 U.S.C. 360j(h)(4)) with a provision that frees agency use of data in PMA's approved 6 or more years before FDA undertakes certain regulatory actions, including device reclassifications. Under section 520(h)(4) of the act, as amended by FDAMA, the agency has supplemented other sources of information that support reclassification of the extracorporeal shock wave lithotripter with data contained in PMA's approved 6 or more years before the date of this proposal. In this instance, FDA has only used data that would have been available to the agency under the superseded four of a kind rule.

Under section 513(f)(2)(B)(i) of the act (21 U.S.C. 360c(f)(2)(B)(i)), the Secretary, for good cause shown, may refer a proposed reclassification to a

device classification panel. The Panel shall make a recommendation to the Secretary respecting approval or denial of the proposed reclassification. Any such recommendation shall contain: (1) A summary of the reasons for the recommendation, (2) a summary of the data upon which the recommendation is based, and (3) an identification of the risks to health (if any) presented by the device with respect to which the proposed reclassification was initiated.

II. Regulatory History of the Device

The extracorporeal shock wave lithotripter intended for the fragmentation of kidney and ureteral calculi is a postamendments device classified into class III under section 513(f)(1) of the act. Therefore, this generic type of device cannot be placed in commercial distribution unless it is reclassified under section 513(f)(2), or is the subject of a PMA or notice of completion of a product development protocol (PDP) under section 515 of the act (21 U.S.C. 360e).

In accordance with section 513(f)(2) of the act, FDA, on its own initiative, is proposing to reclassify this device from class III to class II when intended to fragment kidney and ureteral calculi. FDA referred the proposed reclassification to the Panel for its recommendation on the requested change in classification. This panel meeting was held on July 30, 1998, and is summarized further in Section VI.

III. Device Description

An extracorporeal shock wave lithotripter is a device that focuses ultrasonic shock waves into the body to noninvasively fragment urinary calculi within the kidney and ureter. The primary components of the device are a shock wave generator, high voltage generator, control console, imaging/localization system, and patient table. Prior to treatment, the urinary stone is targeted using either an integral or stand-alone localization/imaging system. Shock waves are typically generated using electrostatic spark discharge (spark gap), electromagnetically repelled membranes, or piezoelectric crystal arrays, and focused onto the stone with either a specially designed reflector, dish, or acoustic lens. The shock waves are created under water within the shock wave generator, and are transferred to the patient's body through a water-filled rubber cushion or by direct contact of the patient's skin with the water. After the stone has been fragmented by the focused shock waves, the fragments pass out of the body with the patient's urine.

IV. Recommendations of the Panel

At a public meeting on July 30, 1998, the Panel unanimously recommended that the extracorporeal shock wave lithotripter indicated for the fragmentation of kidney and ureteral calculi be reclassified from class III to class II. The Panel believed that the special controls of consensus standards, clinical performance testing, labeling restrictions, and physician training restrictions would provide reasonable assurance of the safety and effectiveness of the device.

V. Risks to Health

After considering the information discussed by the Panel during the reclassification proceedings, the published literature, data in PMA applications available to FDA under section 520(h)(4) of the act, as amended by FDAMA, and the Medical Device Reports, FDA believes the following risks are associated with the use of the extracorporeal shock wave lithotripter in the fragmentation of kidney and ureteral calculi.

A. Bleeding

Interaction between the shock waves and internal tissues can result in bleeding within the urinary tract. Lithotripsy-induced bleeding typically presents as either hematuria (blood in the urine) or renal hematoma. Hematuria occurs following most treatments (Refs. 4, 69, and 85), is believed to be secondary to trauma to the renal parenchyma (Ref. 7), and usually resolves spontaneously within 24 to 48 hours of treatment (Refs. 8 and 69). Small, asymptomatic renal hematomas occur with 20 to 25 percent of treatments, which resolve without intervention (Ref. 52). In less than 1 percent of treatments, however, clinically significant intrarenal, subcapsular, or perirenal hematomas occur (Refs. 20 and 50). These patients typically present with severe, chronic flank pain (Refs. 4, 50, 52, and 84), and anuria secondary to renal compression has also been reported (Refs. 62 and 95). Although clinically significant hematomas often resolve with conservative management (Refs. 50, 52, and 84), severe hemorrhage (Refs. 4, 85, and 92) or death (Refs. 66 and 92) has been reported. Management of severe renal hemorrhage includes the administration of blood transfusions (Refs. 50, 52, 81, 85, and 92), percutaneous drainage (Ref. 72), or surgical intervention, which may include nephrectomy (Refs. 4, 50, and 62).

Lithotripsy-induced bleeding is believed to be caused by vessel damage secondary to the collapse of cavitation bubbles at the shock wave focus (Refs. 17 and 65). The risk of serious bleeding is minimized by the use of conservative treatment parameters (Ref. 17) and careful evaluation of the patient post-treatment (Ref. 50).

Patient characteristics associated with increased risk for the development of life threatening hemorrhage include the presence of coagulopathy or the use of anticoagulant therapy (including aspirin) (Refs. 45, 73, 85, and 91), presence of an arterial calcification or vascular aneurysm (Refs. 9, 19, and 91), and poorly-controlled hypertension (Refs. 49 and 50). For some of these high risk patients, however, lithotripsy can still be delivered safely as long as certain precautions are taken. Specifically, patients on anticoagulant therapy can undergo lithotripsy provided that their anticoagulation is temporarily reversed (Refs. 73 and 91). Furthermore, patients with an arterial calcification or vascular aneurysm have been treated without complication provided that the calcification or aneurysm is sufficiently outside of the shock wave path, treatment is limited to a minimum number of low-power shock waves, and the patient is carefully monitored (Refs. 9 and 19).

B. Renal Injury

The focused shock waves delivered by all extracorporeal shock wave lithotripters cause some degree of acute trauma to the treated kidney with associated functional impairment (Refs. 1, 7, 41, and 101). As with bleeding, renal injury is probably secondary to the effects of cavitation at the shock wave focus (Refs. 16, 17, and 82).

It is believed that renal trauma, with associated nephron loss and/or tubule damage, occurs during nearly all lithotripsy treatments (Refs. 1 and 82), is dependent upon the applied shock wave dose (Refs. 74, 82, and 86), and is typically limited to the size of the shock wave focal volume (Ref. 83). While a small region of renal scarring persists at the treated site (Refs. 74 and 86), any associated changes in renal function resolve within 30 days (Refs. 3, 6, 32, and 86). Although infrequently reported and of questionable clinical significance, permanent morphological changes to the kidney have been observed following lithotripsy (Refs. 6 and 74). The risk of renal injury is minimized by delivering fewer, less powerful shock waves (Refs. 70 and 74), and using a lower shock wave repetition rate (Refs. 17 and 86).

Patients with solitary kidneys or pre-existing impairment of renal function may be at increased risk for long-term changes (Refs. 74 and 100). Additionally, although many short-term studies have been published regarding the safe use of extracorporeal shock wave lithotripsy in children (Refs. 53, 55, 69, and 70), questions still exist regarding the long-term effects of shock waves upon the function and growth of the immature kidney (Refs. 15, 27, 70, and 74).

C. Hypertension

Early investigators reported new onset of hypertension in as many as 8 percent of patients between 1 and 2 years following extracorporeal shock wave lithotripsy to the kidney (Refs. 58 and 99). The physiological basis of this finding was theorized to be caused by the Page effect, secondary to the renal fibrosis that occurs following resolution of lithotripsy-induced intraparenchymal hemorrhage (Refs. 52 and 99). Despite the hypertension incidence rates reported by these early studies, however, subsequent research indicates that hypertension is not a risk of lithotripsy. Lingeman et al. noted no difference at 2 years in the rates of new onset of hypertension between patients who received lithotripsy and those who received alternative stone removal therapies, although a small but statistically significant increase in diastolic blood pressure was seen in the lithotripsy group (Ref. 61). In a subsequent report describing 3- and 4-year followup on the same patients, similar outcomes were observed (Ref. 60). In a similar investigation, Vaughan et al. observed no difference in either new onset of hypertension or blood pressure between lithotripsy and nonlithotripsy treated patients 2 years post-treatment (Ref. 98). The results of these controlled studies demonstrate that the development of hypertension is not an actual risk of lithotripsy among normal, healthy patients. However, due to the unknown effects of lithotripsy-induced damage to the growing kidney, concern has been raised that pediatric patients may be at increased risk of developing chronic hypertension (Ref. 74).

D. Cardiac Arrhythmia

Cardiac arrhythmias, most commonly premature ventricular contractions, are generally reported during extracorporeal shock wave lithotripsy at fixed shock wave delivery in 2 to 20 percent of patients (Refs. 14 and 30). While the specific cause of lithotripsy-induced arrhythmias is not fully understood, researchers have postulated several causes, including irritation or mechanical stimulation of the myocardium by the shock wave, autonomic nerve stimulation, or the effects of the intravenous sedatives (Refs. 14 and 43). Arrhythmias resolve spontaneously upon synchronizing the shock waves with the refractory period of the ventricular cycle (i.e., electrocadiograph (ECG) gating) or terminating treatment (Refs. 14, 30, and 102). Although these cardiac disturbances rarely pose a serious risk to the healthy patient, there is the potential for life threatening events to occur in those with a pre-existing history of cardiac disease (Ref. 43). Furthermore, patients with either cardiac pacemakers or implantable defibrillators may be at additional risk due to the possibility of the lithotripter interfering with the function of the pulse generator (Refs. 2, 91, and 97).

The risk of serious cardiac events during lithotripsy can be minimized by monitoring the cardiac activity of all patients during treatment to detect any arrhythmias, and either terminating treatment or switching to an ECG-gated mode of shock wave delivery should an arrhythmia occur (Refs. 59 and 102). Additionally, the risks of lithotripter interference with cardiac pacemakers and implantable defibrillators can be minimized by temporarily reprogramming the pulse generator prior to treatment, verifying the correct function of the pulse generator during and after shock wave delivery, and maintaining sufficient distance between the shock wave path and the pulse generator (Refs. 2, 5, 91, and 97).

E. Urinary Obstruction

Urinary obstruction occurs in up to 6 percent of patients following lithotripsy due to stone fragments becoming lodged in the ureter, and may be the result of either a single stone fragment or the accumulation of multiple small stone particles (i.e., Steinstrasse) (Refs. 24, 48, and 84). Patients with urinary obstruction typically present with persistent pain, and may be at risk of developing hydronephrosis with subsequent renal failure if the obstruction is not promptly treated (Ref. 29). Often, the obstructing fragments pass spontaneously and intervention is not necessary (Refs. 48 and 84). Intervention is indicated in the presence of severe pain, fever, sepsis, or failure of the obstruction to spontaneously resolve, and usually includes ureteroscopic manipulation or retrieval, electrohydraulic or laser lithotripsy, percutaneous nephrostomy drainage, open surgery, or repeat extracorporeal shock wave lithotripsy (Refs. 22, 48, 84, and 93).

F. Infection

Urinary tract infection (UTI) occurs in 1 to 7 percent of patients following extracorporeal shock wave lithotripsy as a result of the release of bacteria from the fragmentation of infected calculi (Refs. 18, 77, 80, and 84). Rarely, pyelonephritis secondary to lithotripsy has been reported (Refs. 77 and 84). Additionally, lithotripsy shock waves can cause local tissue trauma sufficient to permit bacteria to enter the bloodstream from the urinary tract, resulting in sepsis (Refs. 29 and 84). Although the incidence of sepsis following lithotripsy is not common, typically occurring in less than 1 percent of cases (Ref. 31), this complication has the potential for serious consequences (Ref. 84). Patients at greatest risk of developing severe infectious complications include those with pre-existing UTI and infected stones, as well as those who experience urinary obstruction due to the passage of stone fragments (Refs. 29, 38, and 84). Additionally, patients with cardiac disease, including valvular disease and implanted heart valves, and immunocompromised patients are at increased risk for developing bacterial endocarditis following lithotripsy (Ref. 68).

The risk of infectious complications secondary to extracorporeal shock wave lithotripsy can be effectively minimized through the use of prophylactic antibiotics in patients with pre-existing UTI, infected stones, cardiac disease, and compromised immune systems (Refs. 18, 38, 68, and 84).

G. Injury to Adjacent Organs

Because multiple shock waves pass through the patient's body during treatment, extracorporeal shock wave lithotripsy has the potential to cause injury to nontarget organs. Examples of injury to adjacent organs include splenic rupture requiring splenectomy (Refs. 63 and 78), liver hematoma (Ref. 84), and pancreatitis (Ref. 84). In addition, the interaction of shock waves with air-filled organs, such as the lung or bowel, results in hemorrhage secondary to tissue damage (Refs. 36, 65, and 84). Serious injury to adjacent organs is rare, and is minimized through proper patient selection, careful targeting of the shock wave focus, and the use of conservative treatment parameters and retreatment intervals (Refs. 36, 76, and 84).

In addition to the documented risks to adjacent organs described previously, extracorporeal shock wave lithotripsy

potentially represents significant hazards to other nontarget tissues. First, the administration of shock waves to pregnant animals at specific gestational stages has been shown to cause growth disturbances, serious injury, or death to the fetus (Refs. 33 and 71). As a result of these findings, pregnancy is regarded as an absolute contraindication of lithotripsy (Refs. 12, 74, 76, and 91). The medical community has raised the concern that lithotripsy for stones in the lower ureter in women of childbearing potential may cause irreversible damage to the ovary (Ref. 12). Although several investigators have failed to detect ovarian damage in women receiving extracorporeal shock wave lithotripsy to the lower ureter (Refs. 25 and 91), this potential risk has not been fully assessed (Ref. 12). Lastly, Yeaman et al. observed growth plate disturbances in the epiphyses of developing long bones in rats subjected to shock waves, indicating that extracorporeal shock wave lithotripsy may cause growth disturbances in children (Ref. 103). Although these same growth disturbances were not duplicated in a subsequent animal study (Ref. 96), the long-term effects of lithotripsy shock waves upon nontarget pediatric tissues remain unknown.

H. Other Complications

Other reported complications of extracorporeal shock wave lithotripsy include pain/renal colic, skin irritation/bruising, nausea/vomiting, fever, vasovagal syncope, autonomic dysreflexia, embedded stone fragments, and increased stone recurrence rate.

Pain/renal colic and skin irritation/bruising commonly occur during and immediately after treatment (Refs. 22, 24, 47, and 84), are less severe with lithotripters that have less powerful shock waves and larger shock wave generator apertures (Refs. 22, 47, and 79), and typically resolve spontaneously (Ref. 22). Temporary pain/renal colic may also occur secondary to the passage of stone fragments, which is often managed with medication. Chronic pain may be indicative of ureteral obstruction or renal hematoma (Refs. 4, 84, and 92).

Transient nausea and vomiting are occasionally reported immediately after lithotripsy (Refs. 22, 24, and 37), and may be associated with either pain or the administration of sedatives or analgesia.

Fever has been reported after lithotripsy (Refs. 24, 31, 47, and 77), and may be secondary to infection (Ref. 23).

Vasovagal syncope (heart rate suppression concurrent with hypotension) has been reported during lithotripsy, although its incidence is rare (Ref. 44). Researchers attribute this serious condition to either patient anxiety or shock wave stimulation of renal peripheral autonomic nerve fibers, and conclude that the risks of this condition can be minimized by closely monitoring cardiac activity during treatment.

Kabalin et al. demonstrated that while autonomic dysreflexia may occur in spinal cord injured patients during lithotripsy, this condition is effectively treated by terminating shock wave delivery and administering medical therapy (Ref. 42).

Although infrequently noted, stone fragments have the potential to become embedded in the ureteral wall during lithotripsy (Ref. 28). Obstructing submucosal calculi may necessitate endoscopic removal.

Some investigators have observed higher stone recurrence rates following extracorporeal shock wave lithotripsy as compared to alternative stone removal therapies, indicating that retained stone particles may act as a nidus for new stone formation (Ref. 10). However, the magnitude and significance of this finding are unclear and continue to undergo investigation.

VI. Summary of Reasons for Recommendation

After reviewing the data provided by FDA, and after consideration of the open discussions during the Panel meeting and the Panel members' personal knowledge of and clinical experience with the device, the Panel gave the following reasons in support of its recommendation to reclassify the generic type extracorporeal shock wave lithotripter for use in fragmenting kidney and ureteral calculi from class III into class II: (1) The safety and effectiveness of the extracorporeal shock wave lithotripter in the fragmentation of kidney and ureteral calculi has become well-established since approval of the first device in 1984; (2) extracorporeal shock wave lithotripsy is effective in treating most kidney and ureteral calculi, with a typical stone-free rate of 75 percent; and (3) the rates of serious complications from extracorporeal shock wave lithotripsy are low, and can be effectively minimized by: (a) Consensus standards regarding shock wave characterization measurements and general mechanical and electrical safety, (b) clinical performance testing, (c) labeling restrictions, and (d) physician training restrictions (Ref. 94). Based on information presented by FDA, along with the Panel members' personal knowledge and clinical experience, the Panel identified the following risks to health regarding the use of extracorporeal shock wave lithotripsy for the fragmentation of kidney and ureteral calculi: Bleeding and hematoma, renal injury and scarring, cardiac arrhythmia, urinary obstruction, urinary tract infection, and injury to adjacent organs. In addition, the Panel stated that the safety of lithotripsy among certain subgroups is unknown, such as pregnant women, children, and women of childbearing potential with lower ureteral stones. Although hypertension has historically been listed as a potential risk of extracorporeal shock wave lithotripsy, the Panel stated that sufficient evidence now exists to conclude that this condition should not be listed as an actual risk to health.

The Panel believes that the extracorporeal shock wave lithotripter should be reclassified into class II because special controls, in addition to general controls, provide reasonable assurance of the safety and effectiveness of the device, and there is sufficient information to establish special controls to provide such assurance.

VII. Summary of Data Upon Which the Panel Recommendation Is Based

Based on the information discussed by the Panel during the reclassification proceedings, the published literature, and data in premarket approval (PMA) applications available to FDA under section 520(h)(4) of the act, as amended by FDAMA, FDA believes that there is reasonable knowledge of the benefits of the device when used for the fragmentation of kidney and ureteral calculi. Extracorporeal shock wave lithotripsy successfully fragments most urinary calculi. Effectiveness, expressed as the percentage of patients rendered stone-free within 3 months, ranges between 55 to 98 percentage with a typical retreatment rate of 1 to 25 percentage (Refs. 11, 20, 22 to 24, 47, 51, 75, 84, 87, 89, and 93). Successful treatment outcome has been achieved despite the use of different shock wave generator designs (i.e., electrostatic spark discharge, electromagnetically repelled membranes, piezoelectric crystal arrays) and wide range of shock wave characteristics. Similarly, extracorporeal shock wave lithotripter effectiveness is comparable among the different anatomical sites of the upper urinary tract. Specifically, similar stone-free rates are reported for stones in the kidney and the upper, middle, and lower ureter, making extracorporeal shock wave lithotripsy the first-line therapy for most upper urinary calculi (Refs. 11, 13, 21, 46, 66, and 90).

Despite being capable of effectively fragmenting most urinary stones, there

are several limitations to the success of extracorporeal shock wave lithotripsy. Many studies have observed poor effectiveness with both staghorn and large (i.e., greater than 2 centimeters in largest dimension) stones, leading to the recommendation that alternative stone removal therapies should be considered for these cases (Refs. 57, 64, 75, 84, and 88). Furthermore, some stone compositions, particularly cystine calculi, are more resistant to fragmentation than others, and, therefore, may require more shocks than other stone types (Refs. 34 and 91). Because the effectiveness of lithotripsy is predicated on the resulting stone fragments passing from the urinary tract, patients with an obstruction distal to the stone cannot be successfully treated until resolution of the obstruction (Refs. 8, 29, and 57). Stones that are embedded or impacted within the tissue of the kidney or ureter are also not effectively treated with lithotripsy, due to the inability of the stone fragments to pass out of the body (Refs. 29 and 46). Lastly, lithotripsy is not effective in patients with anatomical conditions that prevent targeting of the shock wave focus at the stone, such as severe obesity (Refs. 29 and 91) or orthopedic deformity (Ref. 53).

Although extracorporeal shock wave lithotripsy is effective for the treatment of most ureteral calculi, in some specific instances it is not effective as a first-line therapy. Many authors report poor localization of ureteral stones using ultrasound imaging, making lithotripsy difficult or impossible if the lithotripter does not incorporate or use an x-ray imaging system (Refs. 35, 47, and 90). Additionally, small stones in the middle or lower ureter (i.e., 4 to 6 mm in largest dimension) have a high probability of passing spontaneously (Ref. 67), making the use of lithotripsy unnecessary unless immediate intervention is required.

Since its introduction in the United States in 1984, extracorporeal shock wave lithotripsy has become the preferred treatment for kidney and ureteral calculi (Refs. 56 and 91). Not only is lithotripsy extremely effective, but the overall rate of serious risks from extracorporeal shock wave lithotripsy, primarily clinically significant renal hematoma, severe hemorrhage, chronic renal injury, and sepsis, is low and can be effectively minimized. Treatment is noninvasive, often delivered in an outpatient setting, and can be performed without general or regional anesthesia with many systems (Refs. 37, 56, and 104). Compared to alternative therapies for the removal of urinary calculi, extracorporeal shock wave lithotripsy is either associated with less morbidity (e.g., open surgery, percutaneous nephrolithotomy, ureteroscopy) (Refs. 8, 54, 57, and 84) or increased success (e.g., watchful waiting) (Ref. 67).

Based on the available information, FDA believes that the special controls discussed in section VIII of this document are capable of providing reasonable assurance of the safety and effectiveness of the extracorporeal shock wave lithotripter with regard to the identified risks to health of this device.

VIII. Special Controls

In addition to general controls, FDA believes that the extracorporeal shock wave lithotripter should be subject to the special controls of labeling restrictions and a FDA guidance document to minimize the risks to health identified for this device.

A. Labeling Restrictions

Labeling restrictions can control the risks of bleeding, renal injury, cardiac arrhythmia, urinary obstruction, infection, injury to adjacent organs, and other reported complications by providing information on patient selection, treatment practices, post-treatment followup, and potential adverse events. Specifically, FDA is proposing that extracorporeal shock wave lithotripters be subject to the labeling statements listed in the appendix as a special control, in addition to other required labeling information.

Under 21 CFR 801.109(b)(ii) and section 520(e) of the act, FDA also proposes as described in the guidance document entitled ''Guidance for the Content of Premarket Notifications (510(k)s) for Extracorporeal Shock Wave Lithotripters Indicated for the Fragmentation of Kidney and Ureteral Calculi'' to require the following statement: ''CAUTION: Federal law restricts this device to sale by or on the order of a physician trained and/or experienced in the use of this device as outlined in an appropriate training program.''

B. FDA Guidance Document

Adherence to the FDA guidance document entitled ''Guidance for the Content of Premarket Notifications (510(k)s) for Extracorporeal Shock Wave Lithotripters Indicated for the Fragmentation of Kidney and Ureteral Calculi'' (Ref. 26) can control the risks of bleeding, renal injury, cardiac arrhythmia, urinary obstruction, infection, injury to adjacent organs, and other reported complications by recommending: (1) Conformance to consensus standards, (2) shock wave characterization measurements, (3) assessment of localization accuracy, (4) clinical performance testing, and (5) physician training restrictions for premarket notifications for extracorporeal shock wave lithotripters. These sections of the guidance document correspond to the controls recommended by the Panel.

1. Conformance to consensus standards

The FDA guidance document recommends conformance to the following consensus standards: (1) International Electrotechnical Commission (IEC) 60601–2–36 Medical electrical equipment—Part 2: Particular requirements for the safety of equipment for extracorporeally induced lithotripsy; (Ref. 39) and (2) IEC 61846 Ultrasonics—Pressure pulse lithotripters—Characteristics of fields (Ref. 40).

Conformance with IEC 60601–2–36 can control the risks of bleeding, renal injury, and injury to adjacent organs by requiring that the device accurately localize stones at the shock wave focus and be designed to guard against unintentional shock wave delivery.

Conformance with IEC 61846 can control the risks of bleeding, renal injury, and injury to adjacent organs by providing a standard method for characterizing the lithotripter's acoustic output for the purpose of determining whether its shock wave characteristics are within the range provided by existing systems.

2. Shock wave characterization measurements

Shock wave characterization measurements can control the risks of bleeding, renal injury, and injury to adjacent organs by having each manufacturer assess whether the shock wave characteristics of its lithotripter are within the range provided by existing systems.

3. Assessment of localization accuracy

Assessment of localization accuracy can control the risks of bleeding, renal injury, and injury to adjacent organs by having each manufacturer verify that its device accurately positions stones at the shock wave focus.

4. Clinical performance testing

Clinical performance testing can control the risks of bleeding, renal injury, cardiac arrhythmia, and injury to adjacent organs by verifying that the device accurately locates the target stone, delivers shock waves in accordance with the parameters set by the operator, and does not present an unreasonable risk of injury to the patient. As recommended by the Panel, this testing can take the form of either a small, confirmatory clinical study or a larger clinical investigation of safety and

effectiveness, depending upon the technological characteristics of the particular device (Ref. 94). For extracorporeal shock wave lithotripters that generate shock waves using a similar method to that of legally marketed systems and have comparable shock wave characteristics, a small, confirmatory clinical study should be performed. However, for systems that use a novel method of shock wave generation or have shock wave characteristics that are outside of the range of current devices, a larger clinical investigation is necessary to assess safety and effectiveness.

5. Physician training restrictions

Physician training restrictions can control the risks of bleeding, renal injury, cardiac arrhythmia, urinary obstruction, infection, injury to adjacent organs, and other reported complications by having each manufacturer develop a training program to instruct users of their device on both the operation of the particular lithotripsy system and the general practices for the safe and effective use of extracorporeal shock wave lithotripters (Ref. 76). Manufacturers should inform device users of this physician training restriction with the following labeling statement: ''CAUTION: Federal law restricts this device to sale by or on the order of a physician trained and/or experienced in the use of this device as outlined in a training program.''

IX. FDA's Tentative Findings

The Panel and FDA believe that the extracorporeal shock wave lithotripter should be classified into class II because special controls, in addition to general controls, would provide reasonable assurance of the safety and effectiveness of the device, and there is sufficient information to establish special controls to provide such assurance.

X. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday:

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XI. Environmental Impact

The agency has determined under 21 CFR 25.34(b) that this reclassification action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

XII. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612) (as amended by subtitle D of the Small Business Regulatory Fairness Act of 1996 (Pub. L. 104–121), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4)). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages, distributive impacts and equity). The agency believes that this reclassification action is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the reclassification action is not a significant regulatory action as defined by the Executive Order and so is not subject to review under the Executive Order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Reclassification of the device from class III to class II will relieve manufacturers of the cost of complying with the premarket approval requirements in section 515 of the act. Because reclassification will reduce regulatory costs with respect to this device, it will impose no significant economic impact on any small entities, and it may permit small potential competitors to enter the marketplace by lowering their costs. The agency therefore certifies that this reclassification action, if finalized, will

not have a significant economic impact on a substantial number of small entities. In addition, this reclassification action will not impose costs of $100 million or more on either the private sector or state, local, and tribal governments in the aggregate, and therefore a summary statement of analysis under section 202(a) of the Unfunded Mandates Reform Act of 1995 is not required.

XIII. Request for Comments

Interested persons may, on or before May 10, 1999 submit to the Dockets Management Branch (address above) written comments regarding this document. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects in 21 CFR Part 876

Medical devices.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 876 be amended as follows:

PART 876—GASTROENTEROLOGY–UROLOGY DEVICES

1. The authority citation for 21 CFR part 876 continues to read as follows:

Authority: 21 U.S.C. 351, 360, 360c, 360e, 360j, 360l, 371.

2. § 876.5990 is added to subpart F to read as follows:

§ 876.5990 Extracorporeal shock wave lithotripter.

(a) *Identification*. An extracorporeal shock wave lithotripter is a device that focuses ultrasonic shock waves into the body to noninvasively fragment urinary calculi within the kidney and ureter. The primary components of the device are a shock wave generator, high voltage generator, control console, imaging/localization system, and patient table. Prior to treatment, the urinary stone is targeted using either an integral or stand-alone localization/imaging system. Shock waves are typically generated using electrostatic spark discharge (spark gap), electromagnetically repelled membranes, or piezoelectric crystal arrays, and focused onto the stone with either a specially designed reflector, dish, or acoustic lens. The shock waves are created under water within the shock wave generator, and are transferred to the patient's body through a water-filled rubber cushion or by direct contact of the patient's skin with the water. After the stone has been fragmented by the focused shock waves, the fragments pass out of the body with the patient's urine.

(b) *Classification*. Class II (special controls).

(1) Labeling that contains the statements listed in the appendix in addition to other required labeling information.

(2) FDA guidance document entitled ''Guidance for the Content of Premarket Notifications (510(k)'s) for Extracorporeal Shock Wave Lithotripters Indicated for the Fragmentation of Kidney and Ureteral Calculi.''

APPENDIX TO § 876.5990: Labeling Restrictions

a. Contraindications:

Do not use the device in patients with:

Anatomy which precludes focusing the device at the target stone, such as severe obesity or excessive spinal curvature.

Arterial calcification or vascular aneurysm in the lithotripter's shock wave path.

Coagulation abnormalities (as indicated by abnormal prothrombin time, partial thromboplastin time, or bleeding time) or those currently receiving anticoagulants (including aspirin).

Confirmed or suspected pregnancy.

Urinary tract obstruction distal to the stone.

b. Warnings:

Air-filled interfaces in shock wave path: Do not apply shock waves to air-filled areas of the body, i.e., intestines or lungs. Shock waves are rapidly dispersed by passage through an air-filled interface, which can cause bleeding and other harmful side effects.

Anticoagulants: Patients receiving anticoagulants (including aspirin) should temporarily discontinue such medication prior to extracorporeal shock wave lithotripsy to prevent severe hemorrhage.

Bilateral stones: Do not perform bilateral treatment of kidney stones in a single treatment session, because either bilateral renal injury or total urinary tract obstruction by stone fragments may result. Patients with bilateral kidney stones should be treated using a separate treatment session for each side. In the event of total urinary obstruction, corrective procedures may be needed to ensure drainage of urine.

Cardiac arrhythmia during treatment: If a patient experiences cardiac arrhythmia during treatment at a fixed shock wave repetition rate, shock wave delivery should either be terminated or switched to an ECG-gated mode (i.e., delivery of the shock wave during the refractory period of the patient's cardiac cycle). As a general practice, patients with a history of cardiac arrhythmia should be treated in the ECG-gated mode. (If the system is capable of delivering shock waves at a fixed frequency.)

Cardiac disease, immunosuppression, and diabetes mellitus: Prophylactic antibiotics should be administered prior to extracorporeal shock wave lithotripsy treatment to patients with cardiac disease (including valvular disease), immunosuppression, and diabetes mellitus, to prevent bacterial and/or subacute endocarditis.

Cardiac monitoring: Always perform cardiac monitoring during lithotripsy treatment, because the use of extracorporeal shock wave lithotripsy has been reported to cause ventricular cardiac arrhythmias in some individuals. This warning is especially important for patients who may be at risk of cardiac arrhythmia due to a history of cardiac irregularities or heart failure.

Infected stones: Prophylactic antibiotics should be administered prior to treatment whenever the possibility of stone infection exists. Extracorporeal shock wave lithotripsy treatment of pathogen-harboring calculi could result in systemic infection.

Pacemaker or implantable defibrillator: To reduce the incidence of malfunction to a pacemaker or implantable defibrillator, the pulse generator should be programmed to a single chamber, non-rate responsive mode (pacemakers) or an inactive mode (implantable defibrillators) prior to lithotripsy, and evaluated for proper function post-treatment. Do not focus the lithotripter's shock wave through or near the pulse generator.

c. Precautions:

Impacted or embedded stones: The effectiveness of extracorporeal shock wave lithotripsy may be limited in patients with impacted or embedded stones. Alternative procedures are recommended for these patients.

Radiographic followup: All patients should be followed radiographically after treatment until stone-free or there are no remaining stone fragments which are likely to cause silent obstruction and loss of renal function.

Renal injury: To reduce the risk of injury to the kidney and surrounding tissues, it is recommended that: (1) The number of shock waves administered during each treatment session be minimized; (2) retreatment to the same

kidney/anatomical site occur no sooner than 1 month after the initial treatment; and (3) each kidney/anatomical site be limited to a total of three treatment sessions.

Small ureteral stones: Small middle and lower ureteral stones, 4 to 6 mm in largest dimension, are likely to pass spontaneously. Therefore, the risks and benefits of extracorporeal shock wave lithotripsy should be carefully assessed in this patient population.

Staghorn stones: The effectiveness of extracorporeal shock wave lithotripsy may be limited in patients with either staghorn or large (≤ 20 mm in largest dimension) stones. Alternative procedures are recommended for these patients.

d. Patient Selection and Treatment:

Children: The safety and effectiveness of this device in the treatment of urolithiasis in children have not been demonstrated. Although children have been treated with shock wave therapy for upper urinary tract stones, experience with lithotripsy in such cases is limited. Studies indicate that there are growth plate disturbances in the epiphyses of developing long bones in rats subjected to shock waves. The significance of this finding to human experience is unknown.

Women of childbearing potential: The treatment of lower ureteral stones should be avoided in women of childbearing potential. The application of shock wave lithotripsy to this patient population could possibly result in irreversible damage to the female reproductive system and to the unborn fetus in the undiagnosed pregnancy.

e. Adverse Events:

Potential adverse events associated with the use of extracorporeal shock wave lithotripsy include those listed below, categorized by frequency and individually described:

1. *Potential Adverse Events of Extracorporeal Shock Wave Lithotripsy Categorized by Frequency*:

a. Commonly reported (> 20 percentage of patients): Hematuria, pain/renal colic, skin redness at shock wave entry site.

b. Occasionally reported (1 to 20 percentage of patients): Cardiac arrhythmia, urinary tract infection, urinary obstruction/steinstrasse, skin bruising at shock wave entry site, fever (> 38EC), nausea/vomiting.

c. Infrequently reported (< 1 percentage of patients): Hematoma (perirenal/intrarenal), renal injury.

2. *Description of Adverse Events of Extracorporeal Shock Wave Lithotripsy*:

Cardiac arrhythmia: Cardiac arrhythmias, most commonly premature ventricular contractions, are generally reported during extracorporeal shock wave lithotripsy at fixed shock wave delivery in 2 to 20 percentage of patients. These cardiac disturbances rarely pose a serious risk to the healthy patient, and typically resolve spontaneously upon synchronizing the shock waves with the refractory period of the ventricular cycle (i.e., ECG gating) or terminating treatment.

Fever (> 38 C): Fever is occasionally reported after lithotripsy, and may be secondary to infection.

Hematoma (perirenal/intrarenal): Clinically significant intrarenal or perirenal hematomas occur in < 1 percentage of lithotripsy treatments. Typically patients who experience this complication present with severe flank pain. Although clinically significant hematomas often resolve with conservative management, severe hemorrhage and death have been reported. Management of severe renal hemorrhage includes the administration of blood transfusions, percutaneous drainage, or surgical intervention.

Hematuria: Hematuria occurs following most treatments, is believed to be secondary to trauma to the renal parenchyma, and usually resolves spontaneously within 24 to 48 hours of treatment.

Nausea/vomiting: Transient nausea and vomiting are occasionally reported immediately after lithotripsy, and may be associated with either pain or the administration of sedatives or analgesia.

Pain/renal colic: Pain/renal colic commonly occurs during and immediately after treatment, and typically resolves spontaneously. Temporary pain/renal colic may also occur secondary to the passage of stone fragments, and can be managed with medication.

Renal injury: Extracorporeal shock wave lithotripsy procedures have been known to cause damage to the treated kidney. The potential for injury, its long-term significance, and its duration are unknown.

Skin bruising at shock wave entry site: Skin bruising at the shock wave entry site occasionally occurs after treatment, and it typically resolves spontaneously.

Skin redness at shock wave entry site: Skin redness at the shock wave entry site commonly occurs during and immediately after treatment, and typically resolves spontaneously.

Urinary obstruction/steinstrasse: Urinary obstruction occurs in up to 6 percent of patients following lithotripsy due to stone fragments becoming lodged in the ureter, and may be the result of either a single stone fragment or the accumulation of multiple small stone particles (i.e., steinstrasse). Patients with urinary obstruction typically present with persistent pain, and may be at risk of developing hydronephrosis with subsequent renal failure if the obstruction is not promptly treated. Intervention is necessary if the obstructing fragments do not pass spontaneously.

Urinary tract infection: Urinary tract infection (UTI) occurs in 1 to 7 percent of patients following extracorporeal shock wave lithotripsy as a result of the release of bacteria from the fragmentation of infected calculi, and infrequently results in pyelonephritis or sepsis. The risk of infectious complications secondary to extracorporeal shock wave lithotripsy can be minimized through the use of prophylactic antibiotics in patients with UTI and infection stones.

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Linda S. Kahn,

Deputy Director for Regulations Policy, Center for Devices and Radiological Health.

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DEPARTMENT OF TRANSPORTATION

Federal Highway Administration

23 CFR Part 180

Federal Railroad Administration

49 CFR Part 261

Federal Transit Administration

49 CFR Part 640

[FHWA Docket No. FHWA–98–47–15]

RIN 2125–AE49

Credit Assistance for Surface Transportation Projects

AGENCY: Federal Highway Administration (FHWA), Federal Railroad Administration (FRA), Federal Transit Administration (FTA), U.S. Department of Transportation (DOT).

ACTION: Notice of proposed rulemaking (NPRM); request for comments.

SUMMARY: This document proposes to implement a new program enacted under the Transportation Infrastructure Finance and Innovation Act of 1998 (TIFIA), to provide credit assistance to surface transportation projects. The TIFIA authorizes the DOT to provide secured (direct) loans, lines of credit, and loan guarantees to public and private sponsors of eligible surface transportation projects. Projects will be evaluated and selected by the Secretary of Transportation. Following selections,