

adverse events. Currently, the FDA receives about 200,000 reports to MAUDE each year, and the majority are on paper, which delays entry into the system and analysis for any kind of safety signal, said Dr. Schultz. The FDA has been piloting an electronic reporting program, and is in the process of writing a rule to require electronic reporting, he said.

Once data are being reported and analyzed more quickly, enforcement will be more timely also, he said. It will also let the FDA focus enforcement efforts on the highest-risk products, Dr. Schultz said. "When enforcement is necessary, it needs to be done quickly, accurately, and

in a way that's meaningful and corrects problems," he said.

The FDA also aims to improve its communications to health professionals and consumers—whether the communications are notices about unsafe devices or simply background on safety and efficacy of products. CDRH will redesign its Web site to be more consumer-friendly. It will also take a closer look at how best to give out data—and when—on a potentially faulty device.

CDRH is hoping to accomplish most of its planned "action points" without seeking additional funding, at least in the near term, Dr. Schultz said. ■

# Emergency Trial Rule Under Scrutiny by FDA

BY ELIZABETH MEHCATIE  
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ROCKVILLE, MD. — The Food and Drug Administration is reviewing a decade-old regulation that allows clinical studies of emergency treatments, including automated defibrillator implantation, to be conducted without obtaining in-

formed consent in people with certain life-threatening conditions.

The FDA's reappraisal and proposed revision of the rule were prompted by concerns that current safeguards do not provide enough protection of human subjects, and by comments that the safeguards are too onerous and impede important research.

At present, a narrow exception to the informed consent requirement exists in the case of patients who cannot provide consent because of their conditions and who have no family members available to give consent.

To be exempt from informed consent, an investigation must meet certain criteria, including the following:

- The patient is in a life-threatening situation.
- The available treatments are unproven or not satisfactory.
- Evidence supports the prospect of direct benefit to the individual.

Since the regulation went into effect in October 1996, the FDA has received 56 requests to conduct emergency research under this rule. A total of 21 studies have been conducted, are being conducted, or are about to start enrollment, according to the FDA.

The FDA has issued draft guidance geared toward institutional review boards, clinical investigators, and sponsors developing and conducting emergency research. It also sponsored a public hearing in October on emergency research.

At that hearing, presenters offered examples of emergency research that could not otherwise have been done without the exception.

Although the current rules could be simplified, the exception to informed consent is critical, said Dr. Paul Pepe, professor of surgery, medicine, and public health, and Riggs Family Chair in emergency medicine at the University of Texas Southwestern Medical Center at Dallas.

"Studies of the automated external defibrillator are an example of the tremendous lifesaving potential of emergency treatments," he said. Such studies can also show that treatments that have been widely accepted and appear to be logical may in fact be harmful in some populations, he added. For example, intravenous fluid resuscitation was found to be harmful in certain trauma populations. If these studies had not been done, Dr. Pepe explained, many people would have died.

"Any revisions to current regulations should serve to expand the ability to perform the highest quality emergency research and to enhance patient protections through fairness, openness, and the use of all media that provide explicit detail regarding the research," Dr. Edward P. Sloan and Dr. Charles Cairns said in a statement on behalf of the American College of Emergency Physicians.

The FDA will review written comments on the guidance, as well as comments made at the hearing, to determine whether the rule should be modified. ■

**Other:**

Other adverse effects that were thought to be possibly or probably related to treatment with Lovenox injection, heparin, or placebo in clinical trials with patients undergoing hip or knee replacement surgery, abdominal or colorectal surgery, or treatment for DVT and that occurred at a rate of at least 2% in the Lovenox Injection group, are provided below.

Adverse Event	Dosing Regimen			
	Lovenox Inj. 40 mg q.d. SC n = 1228		Heparin 5000 U q8h SC n = 1234	
	Severe	Total	Severe	Total
Hemorrhage	<1%	7%	<1%	6%
Anemia	<1%	3%	<1%	3%
Echymosis	0%	3%	0%	3%

<sup>1</sup> Excluding unrelated adverse events.

**Adverse Events Occurring at ≥2% Incidence in Lovenox Injection Treated Patients Undergoing Hip or Knee Replacement Surgery**

Adverse Event	Dosing Regimen									
	Lovenox Inj. 40 mg q.d. SC		Lovenox Inj. 30 mg q12h SC		Heparin 15,000 U/24h SC		Placebo q12h SC			
	Severe	Total	Severe	Total	Severe	Total	Severe	Total		
Fever	0%	8%	0%	0%	<1%	5%	<1%	4%	0%	3%
Hemorrhage	<1%	13%	0%	5%	<1%	4%	1%	4%	0%	3%
Nausea	0%	16%	0%	<2%	<1%	3%	<1%	2%	0%	2%
Anemia	0%	16%	0%	<2%	<1%	2%	2%	5%	<1%	7%
Edema	0%	6%	0%	0%	<1%	2%	<1%	2%	0%	2%
Peripheral edema	0%	6%	0%	0%	<1%	3%	<1%	4%	0%	3%

<sup>1</sup> Excluding unrelated adverse events.

<sup>2</sup> Data represents Lovenox Injection 40 mg SC once a day initiated up to 12 hours prior to surgery in 288 hip replacement surgery patients who received Lovenox Injection peri-operatively in an unblinded fashion in one clinical trial.

<sup>3</sup> Data represents Lovenox Injection 40 mg SC once a day given in a blinded fashion as extended prophylaxis at the end of the peri-operative period in 131 of the original 288 hip replacement surgery patients for up to 21 days in one clinical trial.

**Adverse Events Occurring at ≥2% Incidence in Lovenox Injection Treated Patients With Severely Restricted Mobility During Acute Illness**

Adverse Event	Dosing Regimen	
	Lovenox Inj. 40 mg q.d. SC n = 360	Placebo q.d. SC n = 362
	Severe	Total
Dyspnea	3.3	5.2
Thrombocytopenia	2.8	2.8
Confusion	2.2	1.1
Diarrhea	2.2	1.7
Nausea	2.5	1.7

<sup>1</sup> Excluding unrelated and unlikely adverse events.

**Adverse Events in Lovenox Injection Treated Patients With Unstable Angina or Non-Q-Wave Myocardial Infarction:**

Non-hemorrhagic clinical events reported to be related to Lovenox Injection therapy occurred at an incidence of ≤1%. Non-major hemorrhagic episodes, primarily injection site ecchymoses and hematomas, were more frequently reported in patients treated with SC Lovenox Injection than in patients treated with i.v. heparin. Serious adverse events with Lovenox injection or heparin in a clinical trial in patients with unstable angina or non-Q-wave myocardial infarction that occurred at a rate of at least 0.5% in the Lovenox Injection group, are provided below (respective of relationship to drug therapy).

**Serious Adverse Events Occurring at ≥0.5% Incidence in Lovenox Injection Treated Patients With Unstable Angina or Non-Q-Wave Myocardial Infarction**

Adverse Event	Dosing Regimen	
	Lovenox Inj. 1 mg/kg q12h SC n = 1578	Heparin aPTT Adjusted i.v. Therapy n = 1529
	n (%)	n (%)
Atrial fibrillation	11 (0.70)	3 (0.20)
Heart failure	15 (0.95)	11 (0.72)
Lung edema	11 (0.70)	11 (0.72)
Pneumonia	13 (0.82)	9 (0.59)

**Adverse Events Occurring at ≥2% Incidence in Lovenox Injection Treated Patients Undergoing Treatment of Deep Vein Thrombosis With or Without Pulmonary Embolism**

Adverse Event	Dosing Regimen			
	Lovenox Inj. 1.5 mg/kg q.d. SC n = 298		Heparin aPTT Adjusted i.v. Therapy n = 544	
	Severe	Total	Severe	Total
Injection Site Hemorrhage	0%	5%	0%	3%
Injection Site Pain	0%	2%	0%	2%
Hematuria	0%	2%	0%	<1%

<sup>1</sup> Excluding unrelated adverse events.

**Ongoing Safety Surveillance:**

Since 1993, there have been over 80 reports of epidural or spinal hematoma formation with concurrent use of Lovenox Injection and spinal/epidural anesthesia or spinal puncture. The majority of patients had a post-operative indwelling epidural catheter placed for analgesia or received additional drugs affecting hemostasis such as NSAIDs. Many of the epidural or spinal hematomas caused neurologic injury, including long-term or permanent paralysis. Because these events were reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

**Other Ongoing Safety Surveillance Reports:**

Local reactions at the injection site (i.e., skin necrosis, nodules, inflammation, oozing), systemic allergic reactions (i.e., pruritus, urticaria, anaphylactoid reactions), vesiculobullous rash, rare cases of hypersensitivity cutaneous vasculitis, purpura, thrombocytosis, and thrombocytopenia with thrombosis (see WARNINGS, Thrombocytopenia). Very rare cases of hyperlipidemia have been reported, with one case of hyperlipidemia, with marked hypertriglyceridemia, reported in a diabetic pregnant woman; causality has not been determined.

**OVERDOSAGE**

**Symptoms/Treatment:**

Accidental overdosage following administration of Lovenox Injection may lead to hemorrhagic complications. Injected Lovenox Injection may be largely neutralized by the slow i.v. injection of protamine sulfate (1% solution). The dose of protamine sulfate should be equal to the dose of Lovenox Injection injected: 1 mg protamine sulfate should be administered to neutralize 1 mg Lovenox Injection, if enoxaparin sodium was administered in the previous 8 hours. An infusion of 0.5 mg protamine per 1 mg

of enoxaparin sodium may be administered if enoxaparin sodium was administered greater than 8 hours previous to the protamine administration, or if it has been determined that a second dose of protamine is required. The second infusion of 0.5 mg protamine sulfate per 1 mg of Lovenox Injection may be administered if the aPTT measured 2 to 4 hours after the first infusion remains prolonged.

After 12 hours of the enoxaparin sodium injection, protamine administration may not be required. However, even with higher doses of protamine, the aPTT may remain more prolonged than under normal conditions found following administration of heparin. In all cases, the anti-Factor Xa activity is never completely neutralized (maximum about 60%). Particular care should be taken to avoid overdosage with protamine sulfate. Administration of protamine sulfate can cause severe hypotensive and anaphylactoid reactions. Because fatal reactions, often resembling anaphylaxis, have been reported with protamine sulfate, it should be given only when resuscitation techniques and treatment of anaphylactic shock are readily available. For additional information consult the labeling of Protamine Sulfate Injection, USP, products. A single SC dose of 46.4 mg/kg enoxaparin was lethal to rats. The symptoms of acute toxicity were ataxia, decreased motility, dyspnea, cyanosis, and coma.

**DOSE AND ADMINISTRATION**

All patients should be evaluated for a bleeding disorder before administration of Lovenox Injection, unless the medication is needed urgently. Since coagulation parameters are unsuitable for monitoring Lovenox Injection activity, routine monitoring of coagulation parameters is not required (see PRECAUTIONS, Laboratory Tests).

**Note:** Lovenox Injection is available in two concentrations:

1. **100 mg/mL Concentration:** 30 mg / 0.3 mL and 40 mg / 0.4 mL prefilled single-dose syringes, 60 mg / 0.6 mL, 80 mg / 0.8 mL, and 100 mg / 1 mL prefilled, graduated, single-dose syringes, 300 mg / 3.0 mL multiple-dose vials.
2. **150 mg/mL Concentration:** 120 mg / 0.8 mL and 150 mg / 1 mL prefilled, graduated, single-dose syringes.

**Adult Dosage:**

**Abdominal Surgery:** In patients undergoing abdominal surgery who are at risk for thromboembolic complications, the recommended dose of Lovenox Injection is **40 mg once a day** administered by SC injection with the initial dose given 2 hours prior to surgery. The usual duration of administration is 7 to 10 days; up to 12 days administration has been well tolerated in clinical trials.

**Hip or Knee Replacement Surgery:** In patients undergoing hip or knee replacement surgery, the recommended dose of Lovenox Injection is **30 mg every 12 hours** administered by SC injection. Provided that hemostasis has been established, the initial dose should be given **12 to 24 hours** after surgery. For hip replacement surgery, a dose of **40 mg once a day** SC, given initially 12 (±3) hours prior to surgery, may be considered. Following the initial phase of thromboprophylaxis in hip replacement surgery patients, continued prophylaxis with Lovenox Injection 40 mg once a day administered by SC injection for 3 weeks is recommended. The usual duration of administration is 7 to 10 days; up to 14 days administration has been well tolerated in clinical trials.

**Medical Patients During Acute Illness:** In medical patients at risk for thromboembolic complications due to severely restricted mobility during acute illness, the recommended dose of Lovenox Injection is **40 mg once a day** administered by SC injection. The usual duration of administration is 6 to 11 days; up to 14 days of Lovenox Injection has been well tolerated in the controlled clinical trial.

**Unstable Angina and Non-Q-Wave Myocardial Infarction:** In patients with unstable angina or non-Q-wave myocardial infarction, the recommended dose of Lovenox Injection is **1 mg/kg administered SC every 12 hours** in conjunction with oral aspirin therapy (100 to 325 mg once daily). Treatment with Lovenox Injection should be prescribed for a minimum of 2 days and continued until clinical stabilization. To minimize the risk of bleeding following vascular instrumentation during the treatment of unstable angina, adhere precisely to the intervals recommended between Lovenox Injection doses. The vascular access sheath for instrumentation should remain in place for 6 to 8 hours following a dose of Lovenox Injection. The next scheduled dose should be given no sooner than 6 to 8 hours after sheath removal. The site of the procedure should be observed for signs of bleeding or hematoma formation. The usual duration of treatment is 2 to 8 days; up to 12.5 days of Lovenox Injection has been well tolerated in clinical trials.

**Treatment of Deep Vein Thrombosis With or Without Pulmonary Embolism:** In **outpatient treatment**, patients with acute deep vein thrombosis without pulmonary embolism who can be treated at home, the recommended dose of Lovenox Injection is **1 mg/kg every 12 hours** administered SC. In **inpatient (hospital) treatment**, patients with acute deep vein thrombosis with pulmonary embolism or patients with acute deep vein thrombosis without pulmonary embolism (who are not candidates for outpatient treatment), the recommended dose of Lovenox Injection is **1 mg/kg every 12 hours** administered SC or **1.5 mg/kg once a day** administered SC at the same time every day. In both outpatient and inpatient (hospital) treatments, warfarin sodium therapy should be initiated when appropriate (usually within 72 hours of Lovenox Injection). Lovenox Injection should be continued for a minimum of 5 days and until a therapeutic oral anticoagulant effect has been achieved (International Normalization Ratio 2.0 to 3.0). The average duration of administration is 7 days; up to 17 days of Lovenox Injection administration has been well tolerated in controlled clinical trials.

**Renal Impairment:**

Although no dose adjustment is recommended in patients with moderate (creatinine clearance 30-50 mL/min) and mild (creatinine clearance 50-80 mL/min) renal impairment, all such patients should be observed carefully for signs and symptoms of bleeding.

The recommended prophylaxis and treatment dosage regimens for patients with severe renal impairment (creatinine clearance <30 mL/min) are described in the following table (see **CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations** and **PRECAUTIONS, Renal Impairment**).

**Dosage Regimens for Patients with Severe Renal Impairment (creatinine clearance <30 mL/minute)**

Indication	Dosage Regimen
Prophylaxis in abdominal surgery	30 mg administered SC once daily
Prophylaxis in hip or knee replacement surgery	30 mg administered SC once daily
Prophylaxis in medical patients during acute illness	30 mg administered SC once daily
Prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin	1 mg/kg administered SC once daily
Inpatient treatment of acute deep vein thrombosis with or without pulmonary embolism, when administered in conjunction with warfarin sodium	1 mg/kg administered SC once daily
Outpatient treatment of acute deep vein thrombosis without pulmonary embolism, when administered in conjunction with warfarin sodium	1 mg/kg administered SC once daily

**Administration:**

Lovenox Injection is a clear, colorless to pale yellow sterile solution, and as with other parenteral drug products, should be inspected visually for particulate matter and discoloration prior to administration.

The use of a tuberculin syringe or equivalent is recommended when using Lovenox multiple-dose vials to assure withdrawal of the appropriate volume of drug.

Lovenox Injection is administered by SC injection. It must not be administered by intramuscular injection. Lovenox Injection is intended for use under the guidance of a physician. Patients may self-inject only if their physician determines that it is appropriate and with medical follow-up, as necessary. Proper training in subcutaneous injection technique (with or without the assistance of an injection device) should be provided.

**Subcutaneous Injection Technique:** Patients should be lying down and Lovenox Injection administered by deep SC injection. To avoid the loss of drug when using the 30 and 40 mg prefilled syringes, do not expel the air bubble from the syringe before the injection. Administration should be alternated between the left and right antero-

**LOVENOX®**

**(enoxaparin sodium injection)**

lateral and left and right posterolateral abdominal wall. The whole length of the needle should be introduced into a skin fold held between the thumb and forefinger; the skin fold should be held throughout the injection. To minimize bruising, do not rub the injection site after completion of the injection. Lovenox Injection prefilled syringes and graduated prefilled syringes are available with a system that shields the needle after injection.

- Remove the needle shield by pulling it straight off the syringe. If adjusting the dose is required, the dose adjustment must be done prior to injecting the prescribed dose to the patient.



- Inject using standard technique, pushing the plunger to the bottom of the syringe.



- Remove the syringe from the injection site keeping your finger on the plunger rod.



- Orienting the needle away from you and others, activate the safety system by firmly pushing the plunger rod. The protective sleeve will automatically cover the needle and an audible "click" will be heard to confirm shield activation.



- Immediately dispose of the syringe in the nearest sharps container.



- NOTE:**
- The safety system can only be activated once the syringe has been emptied.
  - Activation of the safety system must be done only after removing the needle from the patient's skin.
  - Do not replace the needle shield after injection.
  - The safety system should not be sterilized.
  - Activation of the safety system may cause minimal splatter of fluid. For optimal safety activate the system while orienting it downwards away from yourself and others.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

**Keep out of the reach of children.**

<sup>1</sup> Lepercq J, Conard J, Borel-Derlon A, et al. Venous thromboembolism during pregnancy: a retrospective study of enoxaparin safety in 624 pregnancies. *Br J Obstet Gynecol* 2001; 108 (11): 1134-40.

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