Routes Of Drug Administration

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"This Constitution, and the laws of the United States which shall be made in pursuance thereof; and all treaties made, or which shall be made, under the authority of the United States, shall be the supreme law of the land; and the judges in every state shall be bound thereby, anything in the Constitution or laws of any State to the contrary notwithstanding."
— Article VI of the United States Constitution

THIS STATEMENT, contained in the United States Constitution, is known as the Supremacy Clause and governs the interaction between federal and state governments. It also serves as the foundation for the preemption doctrine which makes federal law paramount to any conflicting state law.

FEDERAL PREEMPTION • Over the years, the Supreme Court has been asked to determine if certain state actions violate this important legal mandate. From *McCulloch v. Maryland,* 17 U.S. 316 (1819), in which the court held that Maryland could not tax a bank chartered by the federal government, to *Riegel v. Medtronic,* 128 S. Ct. 999 (2008), in which the Medical Device Act was found to preempt common law

claims against manufactures whose medical devices had received pre-market Food and Drug Administration (FDA) approval, the court has issued a number of landmark rulings on the topic. On March 4, 2009, the Supreme Court issued another preemption ruling; this decision sent shock waves throughout the pharmaceutical industry.

THE SUPREME COURT • *Wyeth v. Levine*, 555 U.S. ___, 2009 WL 529172, U.S. Vt., March 04, 2009 (NO. 06-1249) involved negligence and failure to warn claims against a drug manufacturer on the basis that an FDA approved label was inadequate under state law. To be more specific, the issues before the Court were whether a state-law duty to provide a stronger warning label interferes with Congress' purpose in entrusting an expert agency with drug labeling decisions and whether state-law claims are preempted because it is impossible for drug manufacturers to comply with both their federal labeling mandates and state-law duties.

The Holding

The Supreme Court resolved both of these questions against the drug manufacturer, noting that the question of preemption must be guided by two cornerstones:

- "The purpose of Congress is the ultimate touchstone in every pre-emption case"; and
- "The historical police powers of the States were not to be superseded by the Federal Act unless that was the clear and manifest purpose of Congress."

Although the FDA is given the power to protect the public's health and assure the safety and reliability of drugs, the court found that subsequent amendments to the Act added a savings clause that indicated state law would only be declared invalid upon a "direct and positive conflict." Since no such conflict existed, the court found that manufacturers remain responsible for updating their labels after FDA approval based upon safety information that becomes available after the drug's initial approval. Also, in keeping with Congress' intent not to specially preempt common law tort suits, the Supreme Court noted that the FDA regarded state law remedies as a complementary form of drug regulation. Therefore, state-related failure to warn lawsuits support the premise that manufacturers and not the federal agency bear the primary reasonability for drug labeling at all times.

THE MEDICAL ISSUE • Whether Congress will try to amend the Food and Drug Act and related legislation to expressly prohibit state court actions in this area remains to be seen. The balance of the article will not discuss the legal implications of *Wyeth v. Levine.* Since it is such an important preemption decision, the case will undoubtedly be the subject of future law review articles and commentaries. Rather, the presentation will focus on the underlying medical issue presented in *Wyeth v. Levine*: routes of drug administration, because the subject is one that is not well understood in the legal community, even though pharmacology plays such an important role in the treatment of patients, and can be an issue in medical malpractice actions.

The Medical Facts

Wyeth is the manufacturer of the drug, Phenergan, an antihistamine used to treat nausea. Diana Levine, a professional musician, suffered from migraine headaches and resultant nausea. The musician visited a clinic for treatment of a migraine and received an intramuscular injection of Phenergan. Later in the day, Levine retuned to the clinic because she continued to suffer nausea and received a second dose of Phenergan. This time the medication was administered through an "i.v. push." The medication was supposed to be injected into her vein, but somehow it found its way into an artery. The result was that the artery and tissues in her arm were severely damaged and died, leading to

gangrene and amputation of her arm. *Levine v. Wyeth,* 944 A.2d 179 (Vt. 2008). The evidence demonstrated that because of the toxic nature of the drug when administered improperly, the medication should not come in contact with an artery; this danger being understood by the manufacturer. It was also known that the i.v. push method of drug administration increased the risk of arterial exposure. In fact, the manufacturer was aware that a number of people over the years had suffered limb amputations from the improper administration of the medication, but the drug's label was never changed to warn against the dangers of the i.v. push method.

ROUTES OF ADMINISTRATION • *Wyeth v. Levine* involves the medical issue as to the differences in the way that drugs may be administered. For instance, what are the distinctions among an intramuscular injection, a peripheral or central line i.v., an i.v. push and transdermal administration of medication?

Pharmaceutical drugs are essential in the treatment of patients, but there are countless ways by which they can be administered. The FDA lists more than 100 different methods in which medication can be introduced into the body. *See,* Center for Drug Evaluation and Research, Data Standards Manual, http://www.fda.gov/cder/dsm/DRG/drg00301.htm.

The technical term for the dispensing of medicine is the "route of administration" which refers to the starting point for the drug's introduction into the body up to the place where it acts upon the target organ or system. Russ, Freeman, and McQuade, Attorneys Medical Advisor, MEDADV, section 30:4 (August 2008).

The way that the body handles medication, through absorption, distribution, metabolism and elimination, is known as pharmacokinetics. Goodman & Gilman, The Pharmacological Basis of Therapeutics (McGraw Hill Companies, 11th Edition), chapter one. Drugs also vary widely in their individual pharmacokinetic properties.

Therefore, the route that a specific drug is given to a patient depends upon a number of factors, particularly the nature of the drug, its pharmacokinetics, and the nature and urgency of the medical condition. While multiple variations exist, the main methods of medication administration are: oral, transdermal, transmucosal, inhalation, and parenteral—which is further divided into subcutaneous, intramuscular, and vascular routes.

Oral (Enteral)

The most common way to give medications is orally, or by mouth, in which the patient swallows a pill or capsule. The enteral route is used primarily for convenience, economy, stability, and patient acceptance. *Concepts in Pharmacotherapy,* The Merck Manual of Diagnosis and Therapy, (18th ed, Merck Research Laboratories, 2006). When ordered by a physician, this method of administration is usually written as p.o. (per os). In this route of delivery, the medication must reach the intestine where it is broken down, absorbed across the intestinal wall, picked up in the blood stream, and delivered to its intended target. These steps, however, take time—up to 30 to 45 minutes between the taking of the medication and its effect. Examples of medication given this route include Lipitor for cholesterol, Keppra for epilepsy and Norvasc for blood pressure.

The potencies and therapeutic effects of a number of medications are reduced when taken orally because of the partial degradation and varying absorption rates across the intestine that occur before the drug reaches its intended target. Time-release medications and pharmaceuticals are designed to produce slow, uniform absorption into the body. Brandon Vogel, *Advances in Drug Delivery Systems,* Modern Drug Discovery, April 2001, Vol. 4 No. 4, pp. 49-50, 52. The variability and unpredictability of the oral route, however, have led pharmaceutical researchers to look for other methods of medication administration.

Transmucosal

The mucosa is the highly vascular lining of all entry ports to the body such as the mouth, nose, rectum, and vagina. Some medications can be applied directly to the mucosa, thereby causing absorption into the blood vessels directly and on to the target organs of the body. This method bypasses the intestines, resulting in the much quicker onset of action. A major benefit of this application is its simplicity; it requires little preparation, supervision, or expertise. The possible disadvantages are localized tissue irritation and burning, and with oral preparations, a disagreeable taste. *Routes of Upload Analgesic Therapy in the Management of Cancer Pain,* Current Topics in Oncology, CancerConsultants.com, http:// professional/ cancerconsultants.com/ccj_pain.aspx?id=23793. Examples of transmucosal medications include nitroglycerine for angina (taken under the tongue), Zomig NS for migraine (as a nasal spray), and rectal Valium for seizure control.

Inhalation

Inhalation of medication, a type of transmucosal approach, is usually administered for respiratory problems such as asthma and severe allergies. With this method, the drug is inhaled through a specialized delivery system into the airways leading to the lungs. Medications administered by this approach frequently use a device known as a metered dose inhaler (MDI). Inhalation provides a better chance of the drug reaching the small airways, thereby increasing the medication's effectiveness. On the other hand, potential problems include large drug particles that could end up in the mouth that are absorbed into the bloodstream, causing increased side effects. Also, smaller particles could move so quickly that they strike the back of the throat, resulting in less of the drug's ability to reach the airways. *Using Inhaled Medications,* Cleveland Clinic Health Systems, http://my.clevelandclinic.org/disorders/Chronic_Obstructive_Pulmonary_Disease_copd/hic_Using_Inhaled_Medications.aspx. Examples of these medications include Advair Diskus for asthma and Combivent for bronchospasm.

Transdermal

Some medication delivery systems are designed to be applied directly to the skin, providing a controlled-release method over several days. In these specifically formulated medications, the drug is slowly absorbed through the skin by the application of a patch imbedded with the drug. Like the transmucosal method, the medication enters the blood stream directly, bypassing the intestinal system. An advantage of this application is that of patient convenience and compliance since the patch usually only needs to be applied once every day or several days rather than taking a pill multiple times during a day. Like the transmucosal route, local skin irritation may occur as a complication. *Routes of Opioid Analgesic Therapy in the Management of Cancer Pain,* supra. Examples of these medications include a Transderm Scopolomine patch (for vertigo and seasickness), Fentanyl (a potent narcotic analgesic), and Flector (an anti-inflammatory agent).

Parenteral

Medications that are delivered by injection with a needle are described as being given by the parenteral route of administration. The three most common categories in this delivery system are subcutaneous, intramuscular, and intravascular. Because all three of these routes bypass the intestinal system and quickly access the vascular system on their way to their target organ, they offer a more rapid onset of action.

Subcutaneous

Subcutaneous injections (written as s.c. in a doctor's order) are those in which a small needle is inserted just under the skin and the medication is injected. This method is used because there is little

blood flow to fatty tissue, and the injected medication is generally absorbed over a longer period of time. *Subcutaneous Injection Guide: Why are Subcutaneous Injections Given?*, HGH News, http://www.hghnews.us/p/Subcutaneous_Injection_Guide_Why_are_subcutaneous_injections_given_175,298,,.html. Examples of pharmaceutical drugs given by this route include insulin for diabetes mellitus, Imitrex for migraine, and Copaxone for multiple sclerosis.

Intramuscular

Intramuscular injections (written as i.m. in a doctor's orders) are injected directly into a large muscle of the body. This route has the added advantage of serving as a storage point for the drug as it is slowly released into the circulatory system. These muscle locations typically are in the upper arm close to the shoulder, the front of the thigh and the buttock. *Intramuscular Injection,* Encyclopedia of Nursing & Allied Health, http://www.enotes. com/nursing-encyclopedia/intramuscular-injection. Hitting a major nerve lying deep within the muscle is a potential complication of intramuscular injections. Examples of these medications include the antibiotic penicillin G and Sandostatin LAR Depot for acromegaly.

Intravascular

Intravascular administration refers to medication injected directly into the circulatory system. This route is the most immediate and provides the quickest onset of action. The two approaches for this method are injection into a vein (written as i.v.) or into an artery (written in the orders as i.a.). Before discussing this route in more detail, however, it would be helpful to briefly describe the circulatory system of the body.

THE CIRCULATORY SYSTEM • This body system is the transportation mechanism by which the blood distributes oxygen and nutrients to the tissues and removes metabolic waste products. The two major components of the circulatory system are the heart and blood vessels.

The Heart

The heart, a muscular organ the size of a fist, is the pump for the whole system, keeping the blood flowing. The systolic blood pressure (the first number in a blood pressure reading, e.g. 120/80 mm/Hg) reflects the pressure generated by the force of each heartbeat. If the heart stops beating, one can lose consciousness within seconds due to the lack of blood flow to the brain and, if no resuscitation is administered to reverse the problem, the person will die within minutes.

The heart has two sets of chambers, the atria and ventricles, which are separated by valves. With a right side and a left side, there are a total of four chambers in the heart. Blood returns to the heart from the body into the right atrium, then flows to the right ventricle. Blood from the right ventricle is then pumped to the lungs where the carbon dioxide waste carried by the red blood cells is exchanged for the incoming oxygen (brought in by the lungs from the outside environment). This oxygenated blood is pumped back to the left side of the heart, entering the left atrium, then the left ventricle, and finally pumped out to the organs and tissues of the body.

Blood Vessels

This second part of the circulatory system is divided into arteries and veins. Arteries are thick, muscular vessels that carry the oxygenated enriched blood from the left ventricle of the heart out to the periphery of the body. As an artery reaches its destination, such as the arm, it divides and subdivides into smaller and smaller vessels, down to the smallest, termed arterioles. In the target tissues, the arterioles further subdivide into capillaries, microscopic in size. At the capillary level, oxygen and nutrients are delivered to the tissues. Waste products from the cells and tissues, along with carbon dioxide, are picked up and transported to the venous side.

Blood flows first though the smaller venules, then small veins and finally the larger veins of the body, much like a large river as it increases in size from the tributaries that feed it. The large veins then dump the blood back into the right atrium and the cycle starts over again.

In addition to the type of oxygenated blood they carry, and the thickness and construction of the vessel wall, arteries and veins differ in how much pressure they carry. Arteries are the high-pressure side of the system; veins are low pressure.

Intravenous

Intravenous (i.v.) delivery of a drug, therefore, involves the administration of a drug into a vein and the medication is diluted by the blood before it reaches its target organ. Intravenously administered drugs can be given slowly by infusion or rapidly by syringe. With the slow infusion method, a short catheter or butterfly needle is inserted into a vein and connected by tubing to an i.v. bag. The bag contains a saline solution with the medication dissolved in the fluid. In another approach, the drug may be "piggy-backed" from a smaller bag into the larger i.v. bag. Which ever method is used, the drug is then "dripped" slowly into the vein, usually by means of a pump which controls the rate of infusion. This method is most useful with antibiotics or chemotherapy given over hours or days. The i.v. can be placed in a location distant to the heart such as the hand or arm (even the foot or head if necessary), or close to the heart in the subclavian vein just beneath the collar bone, termed a central line.

Long-term i.v. therapy over days to months is accomplished through a peripherally inserted central catheter (PICC line). With a PICC line, a catheter is inserted in a vein in the arm and threaded centrally to the large veins emptying into the right atrium of the heart.

If a more rapid delivery system is needed, the medication can be administered directly into the vein through a syringe without the i.v. bag—this is the "i.v. push." Veins used in this method can be either those peripherally, located in the hand and arm, or centrally, close to the heart such as the subclavian vein. Which of these venous locations are used depends upon the urgency of the situation and the patient's cardiovascular stability.

Intra-arterial

Intra-arterial (written as i.a. in an order) injection is not a usual route of administration for most medications because the drug will be quickly transported in large amounts to a localized area of the body. The potential consequence of this action is vascular and tissue damage and death "downstream" from the injection site, such as that which tragically occurred to Diana Levine. One application of intra-arterial injection is for dissolving a blood clot in an artery with tissue plasminogen activator (t-PA).

CONCLUSION • The central medical issue in *Levine v. Wyeth* concerns the improper way that Phenergan, a medication used for treatment of nausea, was given to a patient, leading to the amputation of her arm. The fact that each pharmaceutical drug requires its own specific route of administration is understood by medical providers, but is not well appreciated in the legal community or by the average person. The specific route required—oral (enteral) or injection (parenteral); subcutaneous or intramuscular; intravenous drip or push; transdermal or transmucosal—depends upon a number of factors. These factors include the characteristics of the drug, its pharmacokinetics, the medical problem being treated, and the urgency to get the drug into the patient. This overview describes the most commonly used routes of medication administration in order to provide counsel with a basis of understanding the topic.

PRACTICE CHECKLIST FOR
Routes Of Drug Administration

- Medications play a vital role in the treatment of patients, but there are countless ways by which they can be administered. The technical term for the administration of medicine is the "route of administration," which refers to the starting point for the drug's introduction into the body up to the place where it acts upon the target organ or system.

- The route chosen to give a specific drug to a patient depends upon a number of factors, including the nature of the drug, its pharmacokinetics, and the patient with respect to the nature and urgency of the medical condition. While multiple variations exist in the way that medications are administered, the main methods are: oral, transdermal, transmucosal, inhalation, and parenteral, which is further divided into subcutaneous, intramuscular, and intravascular routes.

- The oral or enteral route, whereby the patient swallows a pill or capsule, is the most common way to administer medications. Because the oral route requires absorption by the intestine, it is the slowest and least reliable method. This route of administration is used primarily for convenience, economy, stability, and patient acceptance.

- The transmucosal and transdermal methods involve applying the medication to the mucosa (the highly vascular lining of all entry ports to the body such as the mouth, nose, rectum, and vagina) or the skin. This route by-passes the intestine, resulting in a more rapid and reliable delivery system.

- Inhalation of medication is usually administered for respiratory problems such as asthma and severe allergies. With this method, the drug is inhaled through a specialized delivery system into the airways leading to the lungs.

- In parenteral administration, the medication is delivered by an injection; these methods are subcutaneous, intramuscular, and intravascular:

__ Subcutaneous (s.c.) injections are those in which the needle is inserted just under the skin;
__ Intramuscular (i.m.) injections are given into large muscles in the arm or leg;
__ Intravascular administration refers to the medication injected directly into the circulatory system, providing the route which is most rapid in onset. The drug can be injected into a vein (i.v.) either slowly by i.v. drip, or rapidly by i.v. push through a syringe. With the exception of t-PA, injections into an artery (i.a.) are usually not done because of possible resulting tissue damage and death.

Appendix

Comparison Of Enteral And Parenteral Routes Of Drug Administration

The following table compares and contrasts the two major routes of drug administration: oral (enteral) and injection (parenteral).

ROUTE	Absorption Pattern	Special Utility	Precautions
Enteral (oral)	Variable, depend on many factors	Most convenient and economical; usually more safe	Requires patient compliance, bioavailability may be erratic and incomplete
Parenteral (injection)			
• *Subcutaneous*	Prompt, use aqueous solutions	Suitable for some poorly soluble suspensions and some slow release	Not suitable for large volumes, possible pain and tissue death from irritating substances
• *Intramuscular*	Prompt with aqueous solutions; slow and sustained with repository drugs	Suitable for moderate volumes, oily solutions, and some irritating substances	Not with anticoagulant therapy; may interfere with some results
• *Intravenous*	Avoids intestinal absorption; rapid onset; useful for large volumes, irritating substances or complex mixtures when diluted	Useful in emergency, can adjust dosage easily and quickly; required for large molecular drugs	Increase risk of adverse effects; must inject solutions slowly as a rule; not suitable for oily solutions or poorly soluble substances

(Modified from Goodman & Gilman's The Pharmacological Basis of Therapeutics (11th ed.))