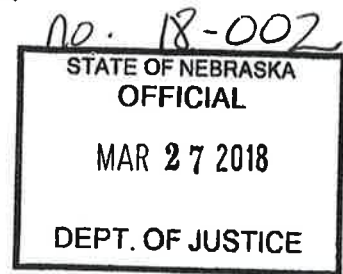




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DOUGLAS J. PETERSON
ATTORNEY GENERAL

SUBJECT: Constitutionality of LB 117, the Investigational Drug Use Act, Under the Supremacy Clause of the U.S. Constitution

REQUESTED BY: Senator Mike Hilgers
Nebraska State Legislature

WRITTEN BY: Douglas J. Peterson, Attorney General
Lynn A. Melson, Assistant Attorney General

You have requested an opinion from this office to address your concerns whether LB 117, the Investigational Drug Use Act, "if enacted into law, would be preempted by the Food, Drug, and Cosmetic Act and the Supremacy Clause of the Constitution." For the reasons set forth below, we think it is likely that one or more of the provisions of LB 117 could be preempted by federal law.

BACKGROUND

As described by the principal introducer of LB 117, Senator Hilkemann, this bill "allows eligible patients under the Act to be treated with any drug, biological product, or device that has successfully completed Phase 1 of a clinical trial but has not yet been approved for general use by the USFDA [United States Food and Drug Administration, or "FDA"] and remains in a clinical trial approved by the USFDA." Committee Records on LB 117, 105th Neb. Leg., 1st Sess. (Jan. 27, 2017) (Introducer's Statement of Intent). He also notes that such an act is more commonly called a "Right to Try" act.

Among its provisions, LB 117 sets out certain criteria for eligible patients, including having an advanced illness, having a recommendation from a treating physician, and giving written, informed consent. Terms such as “eligible patient,” “advanced illness,” “investigational drug” and “written, informed consent” are defined. LB 117, § 2. Under the bill, a manufacturer may, but is not required to, provide the investigational drug, biological product, or device for treatment. LB 117, § 5. Section 11 of the bill further provides that it does not create a private cause of action against the manufacturer of an investigational drug or device for harm to the patient if the manufacturer has complied in good faith with the provisions of LB 117. The patient's health insurance carrier is not obligated to pay for such treatments. The Division of Public Health [of the Nebraska Department of Health & Human Services] may not take any action against the license of a health care provider based solely on the provider's recommendation that the patient use an investigational drug, biological product, or device which has not yet been approved by the FDA, and the State of Nebraska will not block the patient's access to such medical treatment. LB 117, §§ 8-10.

According to one source, “right to try” acts have been enacted in 38 states since 2014. <http://righttotry.org/faq/>. (last accessed on 3/19/18). The provisions of these acts vary from state to state. However, all are based on the premise of allowing terminally ill patients to access investigational drugs and devices that have passed the first phase of clinical trials required for approval by the FDA.

Federal legislation concerning the access by patients with advanced or terminal illnesses to investigational drugs has also been proposed. The Senate passed S. 204, the “Right to Try Act of 2017” on August 3, 2017. A somewhat different “Right to Try Act of 2018”, H.R. 5247, was passed by the House on March 21, 2018.

FEDERAL FOOD, DRUG AND COSMETIC ACT

Prescription drugs, biological products and medical devices are subject to the comprehensive regulation of the Food and Drug Administration (“FDA”) pursuant to the Federal Food, Drug, and Cosmetic Act (“FDCA”), 21 U.S.C. §§ 301 *et seq.* Relevant to this opinion are the statutory and regulatory provisions pertaining to new or investigational drugs. “No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) of this section is effective with respect to such drug.” 21 U.S.C. § 355(a) (2017). In other words, a new drug product cannot be marketed until the FDA determines that the drug is safe and effective and approves an application. 21 U.S.C. § 355(b) (2017). Congress has created an exemption for new drugs “intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs.” 21 U.S.C. § 355(i) (2017). This provision allows studies or clinical trials to be conducted under an investigational new drug application submitted by the drug's manufacturer or sponsor. That investigation process involves several phases, including the Phase 1 clinical trial referenced in LB 117. See 21 C.F.R. Part 312.

We note that biological products can also be drugs and are generally subject to the same statutory and regulatory requirements that apply to drugs. See 42 U.S.C. § 262(j) (providing that the FDCA generally applies to biological products). The FDA also regulates the sale of medical devices pursuant to the Medical Device Amendments of 1976, *codified at* 21 U.S.C. §§ 360c to 360k. There is a requirement of premarket approval for new medical devices as there is for new drugs.

The FDCA also provides for remedies for violation of its provisions, including injunctive relief, criminal prosecution and seizure or forfeiture. See 21 U.S.C. § 331 (prohibited acts), § 332 (injunction proceedings) and § 333 (civil and criminal penalties).

DISCUSSION

You have asked whether LB 117, if enacted, would be preempted by federal law. The Supremacy Clause of the U.S. Constitution provides that the laws enacted by the federal government shall be the "supreme law of the land." U.S. Const. art. VI, c. 2. "Federal preemption arises from the Supremacy Clause of the U.S. Constitution and is the concept that state laws that conflict with federal law are invalid." *In re Application of Lincoln Electric System*, 265 Neb. 70, 76, 655 N.W. 2d 363, 369 (2003), *cert. denied* 539 U.S. 943, 954. Federal regulations can also preempt state law. *Louisiana Public Service Comm'n v. F.C.C.*, 476 U.S. 355 (1986).

"There are three varieties of preemption: express, implied, and conflict preemption." *In re Application of Lincoln Electric System*, 265 Neb. at 76, 655 N.W.2d at 369. "Express preemption arises when congress has explicitly declared federal legislation to have a preemptive effect." *Id.* Absent express preemptive language, a federal statute or regulation may impliedly preempt state law when the language reveals an intent to completely occupy a legislative field. *Zannini v. Ameritrade Holding Corp.*, 266 Neb. 492, 667 N.W.2d 222 (2003). State law is also impliedly preempted if it actually conflicts with federal law. *Id.*

"Consideration under the Supremacy Clause starts with the basic assumption that Congress did not intend to displace state law." *Maryland v. Louisiana*, 451 U.S. 725, 746 (1981). "Pre-emption occurs when Congress, in enacting a federal statute, expresses a clear intent to pre-empt state law, when there is outright or actual conflict between federal and state law, where compliance with both federal and state law is in effect physically impossible, where there is implicit in federal law a barrier to state regulations, where Congress has legislated comprehensively, thus occupying an entire field of regulation" *Louisiana Public Service Comm'n*, 476 U.S. at 368-69. (internal citations omitted).

We note that LB 117 would apply to investigational drugs, biological products and devices that have successfully completed phase one of a clinical trial, but are not yet approved by the FDA. LB 117, § 2. We are aware of no appellate cases which directly address the issue of federal preemption as it may apply to state "right to try" laws. In a

2007 case, the Court of Appeals for the District of Columbia Circuit considered whether terminally ill patients had a fundamental right protected by the due process clause to have access to investigational drugs. *Abigail Alliance for Better Access to Developmental Drugs v. Eschenbach*, 495 F.3d 695 (D.C. Cir. 2007), *cert. denied*, 552 U.S. 1159 (2008). An organization of terminally ill patients and their supporters sought to enjoin the FDA from barring the sale of these experimental drugs not yet approved by the FDA for public use. The Court held that there was no fundamental right to access investigational drugs and also rejected the Alliance's arguments concerning three common law doctrines: the doctrine of necessity, the tort of intentional interference with rescue, and the right to self-defense. This case was decided prior to the enactment of state "right to try" laws and such laws were not at issue. Therefore, there was no discussion of federal preemption.

The *Abigail Alliance* court made note of the Supreme Court's decision in *United States v. Rutherford*, 442 U.S. 544 (1979) in which terminally ill patients sued to enjoin the federal government from interfering with the interstate shipment and sale of Laetrile, a drug which had not yet been approved by the FDA. The Court found "[t]hat the Act [FDCA] makes explicit provision for carefully regulated use of certain drugs not yet demonstrated safe and effective reinforces our conclusion that no exception for terminal patients may be judicially implied." *Id.* at 559. Again, this case predates the enactment of state "right to try" laws and does not directly address federal preemption of state law claims or defenses.

While there appear to be no appellate cases which address the preemption of state "right to try" laws, there are numerous cases in which courts have addressed federal preemption of other state law claims. Certain claims with regard to medical devices may be expressly preempted. Congress has expressed, as part of the Medical Device Amendments of 1976, an intent to preempt certain state laws pertaining to medical devices. 21 U.S.C. § 360k(a) provides that no state "may establish or continue in effect with respect to a device intended for human use any requirement—(1) which is different from, or in addition to, any requirement applicable under this chapter to the device, and (2) which relates to the safety or effectiveness of the device or to any other matter included in a requirement applicable to the device under this chapter." An exception to this language exists where the Secretary, on application of the state, has by regulation exempted the state in limited and specific circumstances.

The degree of federal oversight of medical devices varies with the type of device at issue. Certain classes of devices must undergo a federal premarket approval process. Whether a state law claim is preempted by the Medical Devices Amendments would then depend on several factors, including the type of device at issue and the nature of the state law claim. The United States Supreme Court has employed a two-step analysis to determine whether state law claims with regard to medical devices are preempted. *Riegel v. Medtronic, Inc.*, 552 U.S. 312 (2008). In *Riegel*, the Court first considered whether the federal government had established requirements applicable to the balloon catheter manufactured by the defendant and then whether the plaintiff's common law claims were based on state requirements that were "different from, or in addition to" the federal ones

and that related to safety and effectiveness. *Id.* at 321-322. The Court held that the state common-law claims of negligence, strict liability, and implied warranty were preempted as to this device. The Court also explained that certain medical devices were grandfathered and exempt from premarket approval and that certain new devices need not undergo premarket approval if the FDA finds they are substantially equivalent to another device exempt from premarket approval. The FDA's review of devices for substantial equivalence is known as the § 510(k) process. *Id.* at 317-319. Claims pertaining to these devices might not be preempted.

As explained above in our general discussion of the FDCA, federal law does allow studies or clinical trials to be conducted under an investigational new drug application. Similarly, the manufacturer of certain medical devices may apply for FDA authorization to use a device for clinical testing pursuant to an investigational device exemption or IDE. 21 U.S.C. § 360j(g). We note that a California court has held that this IDE approval of a medical device is similar to premarket approval such that some state law claims pertaining to these investigational devices are preempted by federal law. *Robinson v. Endovascular Technologies, Inc.*, 190 Cal. App. 4th 1490, 119 Cal. Rptr. 3d 158 (Ct. App. 6th Dist. Cal. 2010).

Particular state law claims may also be impliedly preempted by the Medical Device Amendments. For example, state law claims pertaining to a medical device, that was reviewed under the § 510(k) process and not expressly preempted, may still be impliedly preempted. In *Buckman Co. v. Plaintiffs' Legal Committee*, 531 U.S. 341 (2001), the Supreme Court held that plaintiffs' state law claims that a device manufacturer made fraudulent representations in its application filed with the FDA were in conflict with and, therefore, impliedly preempted by the FDCA as amended by the Medical Device Amendments. The conflict arose from the fact that federal law empowered the FDA to punish and deter fraud with regard to such applications.

We have found no express language in the FDCA which preempts state laws pertaining to investigational drugs or biological products. With regard to provisions of LB 117 pertaining to investigational new treatments, a court would then consider whether Congress has "occupied the field" (implied or field preemption) and whether it would be impossible to comply with both state and federal law (conflict preemption).

There are a number of cases which address whether certain state law claims, such as state common law tort claims, are impliedly preempted by the FDCA. For example, in *Wyeth v. Levine*, 555 U.S. 555 (2009), the Supreme Court found that a patient's state law failure-to-warn claim against a brand manufacturer of antihistamine, for failing to adequately warn of dangers of administering the drug intravenously, was not preempted by federal law. While the manufacturer argued that it was impossible to comply with both federal labeling duties under the FDCA and state law duties, the Supreme Court disagreed and held that compliance with the state law duty to warn would not obstruct the purposes and objectives of federal drug labeling regulation.

Two years later, in *PLIVA, Inc. v. Mensing*, 564 U.S. 604 (2011), the Supreme Court distinguished *Wyeth* and noted differences in the federal drug labeling requirements that applied to generic drug manufacturers as compared to brand name drug manufacturers. As the manufacturer in *PLIVA* could not have changed its label without prior FDA approval, compliance with both state and federal requirements was impossible. Due to this conflict, the Court held that federal law preempted state law failure-to-warn claims against generic manufacturers.

It thus appears that, in considering the preemptive effect of the FDCA with regard to a provision of a state “right to try” law such as LB 117, a court would carefully evaluate each claim or defense asserted under the state law and determine whether that claim or defense was preempted by one of the many provisions of the FDCA and the regulations which implement it. In our view, although LB 117, §§ 5 and 6 allow manufacturers of investigational new drugs and biological products to make those treatments available to eligible patients, a defense based on that state law provision may well be impliedly preempted by the provisions of the FDCA which prohibit any person from placing into interstate commerce any new drug which has not yet received FDA approval. 21 U.S.C. § 355(a). Although there is an absence of case law addressing the issue, it is likely that a court would find that Congress and the FDA, through existing federal statutes and regulations concerning early or expanded access to investigational drugs, have “occupied the field” such that LB 117, §§ 5 and 6 are preempted or that those provisions of LB 117 are preempted through conflict preemption. With regard to investigational devices, state law claims may well be expressly preempted.

We point out that the FDA website has a statement regarding “right to try” legislation under the heading “FDA and Marijuana: Questions and Answers.” “The FDA has not taken a position on any particular state ‘Right to Try’ bill. The FDA works with companies to provide patients access to experimental therapies through enrollment in clinical trial or through the expanded access provision described in the FDA’s statute and regulations.” <https://www.fda.gov/newsevents/publichealthfocus/ucm421168.htm>. (last accessed on 3/19/18).

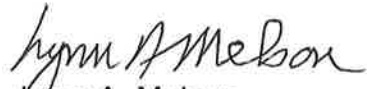
In addition, several law review authors have expressed the opinion that at least some of the provisions of the various “right to try” laws are likely preempted by federal law. “Perhaps the most crucial limitation that Indiana and other state right-to-try legislation may face is the possibility of federal preemption. It appears likely that the FDA could supersede these attempts by state policymakers if they decided to challenge right-to-try legislation.” Howard, *Accessing Indiana's Right-To-Try Law: Is It Enough To Expand Access For Terminally Ill Patients?*, 14 IND. HEALTH L. REV. 267 (2017). See also, Note, *The Right to Try: An Overview of Efforts to Obtain Expedited Access to Unapproved Treatment for the Terminally Ill*, 70 FOOD & DRUG L.J. 617 (2015); Note, *Patients Battle The FDA*, 55 DUQ. L. REV. 397 (2017); and Adriance, *Fighting for the “Right to Try” Unapproved Drugs: Law As Persuasion*, 124 YALE L.J. FORUM 148 (2014).

CONCLUSION

We have found no case law concerning the state "right to try" laws which have been recently adopted by a number of states. However, based on our review of other Supremacy Clause cases, we think a court may well find one or more provisions of LB 117 to be preempted by federal law. We think the provision of § 5, which allows manufacturers to make investigational drugs and devices available to eligible patients, is the most likely to be found preempted by the FDCA and the regulations which implement it.

Sincerely,

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Approved by:


Attorney General
pc. Patrick J. O'Donnell
Clerk of the Nebraska Legislature