No. SC88890

IN THE SUPREME COURT OF MISSOURI

CORTEZ STRONG,

Respondent/Cross-Appellant,

v.

AMERICAN CYANAMID COMPANY,

Appellant/Cross-Respondent.

Transfer from the Missouri Court of Appeals
Eastern District

BRIEF FOR THE UNITED STATES AS AMICUS CURIAE

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PRELIMINARY STATEMENT

The United States respectfully submits this amicus brief to assist this Court in understanding the Food and Drug Administration's longstanding interpretation of its own regulations, and to urge the Court to hold that it is the responsibility of the trial court itself, rather than the jury, to interpret federal regulations consistent with the deference courts owe to a federal agency's interpretation.

Pursuant to federal statute, "[t]he Solicitor General, or any officer of the Department of Justice, may be sent by the Attorney General to any State or district in the United States to attend to the interests of the United States in a suit pending in a court of the United States, or in a court of the State, or to attend to any other interest of the United States." 28 U.S.C. 517.

INTEREST OF THE UNITED STATES

This case concerns the oral polio vaccine, which "has resulted in the virtual eradication of wild poliovirus in the Western Hemisphere." In re Sabin Oral Polio Vaccine Prods. Liab. Litig., 763 F. Supp. 811, 813 (D. Md. 1991) (Sabin II), aff'd, 984 F.2d 124 (4th Cir. 1993). The federal government has played an important regulatory role in this story.

Section 351 of the Public Health Service Act (42 U.S.C. 262), prohibits the introduction into interstate commerce of any biological product without a biologics license. The oral polio vaccine (OPV) is a biological product covered by the statute. The U.S. Food and Drug Administration (FDA), an agency within the U.S. Department of Health and Human Services (HHS), is charged under the statute with issuing regulations that establish "requirements for

the approval, suspension, and revocation of biologics licenses." 42 U.S.C. 262(a)(2)(A). In 1987, the time relevant to this action, FDA regulations specific to OPV manufacture were found at 21 C.F.R. 630.10-630.17. The regulations established a variety of requirements for testing and documentation by the manufacturer in the course of production of the vaccine.

The interest of the United States in this appeal is twofold. First, the United States has an interest in the correct interpretation of its own regulations. At trial, Mr. Thomas Bozzo, a former FDA official, was permitted to testify that, in his opinion, the true meaning of FDA's regulations was different from the agency's longstanding interpretation. The Court of Appeals held that it was permissible to allow the jury, rather than the court, to decide what the regulations meant and for the jury to base its interpretation on Mr. Bozzo's testimony. Second, the United States itself has been sued in actions alleging that the oral polio vaccine caused injury or death. The United States has an interest in ensuring that causation be proved under an appropriate standard and by competent evidence, rather than speculation.

STATEMENT

1. The history of the oral polio vaccine is discussed in Graham v. American Cyanamid Co., 350 F.3d 496 (6th Cir. 2003), cert. denied, 541 U.S. 990 (2004). Briefly, in the 1950s, Dr. Jonas Salk developed the first licensed polio vaccine containing dead or inactivated polio virus. Known as inactivated polio vaccine (IPV), it was administered by injection. At the same time that Dr. Salk was developing IPV, Dr. Albert Sabin participated in the development of a polio virus vaccine to be administered orally. Oral polio vaccine (OPV) was developed from live polio virus that was weakened, but not killed, and it was

believed to have several advantages over IPV, including lifetime immunity for recipients. Like all vaccines developed from live viruses, however, OPV had risks. For example, on rare occasions, the virus reproduced in the intestinal tract can revert to the virulent form. Id. at 499-500; see In re Sabin Oral Polio Vaccine Prods. Liab. Litig., 743 F. Supp. 410, 412 (D. Md. 1990) (Sabin I), aff'd, 984 F.2d 124 (4th Cir. 1993) ("Like other live virus vaccines (such as those used for smallpox and yellow fever), OPV stimulates immunity by inducing a mild infection in vaccinees. Thus, a person vaccinated with OPV or a person who comes into close contact with the vaccine's virus (usually by exposure to the vaccinated person) may develop polio."). A polio infection contracted in such a manner is referred to as vaccine-associated paralytic poliomyelitis (VAPP).

In 1958 and 1959, clinical trials were performed with the oral polio vaccine, and, in 1960, the Surgeon General authorized the use of OPV, derived from strain material developed by Dr. Sabin, in the United States. The polio virus has three types – Types I, II, and III. In 1963, the federal government granted American Cyanamid and its division, Lederle Laboratories, a license to manufacture a "trivalent" vaccine called "Orimune," which responds to all three polio virus types. Graham, 350 F.3d at 500.

OPV is created by taking a strain and injecting small portions into monkey kidney cell cultures, a process known as a "tissue culture passage." That process leads to the growth of more virus. After one or more additional tissue culture passages, "production seeds" are created. Small portions of the production seeds are periodically injected into monkey kidney cell cultures to create monopools of vaccine for each of the three types of polio. The manu-

facturer blends together monopools for each of the vaccine types, resulting in a trivalent lot that is used to produce the vaccine. See Graham, 350 F.3d at 500.

To put this graphically: strain → intermediate material → production seeds → monopools → trivalent lots. The vaccine doses that are administered to individuals come from the blended trivalent lots.

Federal regulations required licensees to test production seeds and monopools to ensure that their neurovirulence was no greater than a reference standard. 21 C.F.R. 630.10(b)(4) (1987 ed.) ("No seed virus shall be used for the manufacture of poliovirus vaccine unless its neurovirulence in Macaca monkeys is no greater than that of the Reference Attenuated Poliovirus distributed by the Bureau of Biologics Research and Review.").

2.a. The present litigation is a products-liability action against American Cyanamid, the manufacturer of Orimune. The plaintiff, Cortez Strong, alleges that he developed partial paralysis after receiving his second dose of Orimune in 1987, when he was four months old. He claims that American Cyanamid violated FDA regulations regarding the manufacture and testing of the vaccine. He also claims that the company was negligent and that Orimune was defective, resulting in his VAPP.

At trial, the plaintiff introduced the testimony of Thomas Bozzo, a former official at FDA, about whether American Cyanamid had complied with the regulatory requirements. Mr. Bozzo testified that American Cyanamid, in his opinion, had violated FDA's regulations in certain ways. Slip op. at 5-6. With respect to causation, Mr. Bozzo testified that "if you omit safety tests, then you raise the possibility of a product being unsafe." Id. at 17. He also

testified that "if the product was inadequately tested for neurovirulence, then it's possible that the product simply contained particles of neurovirulent virus, and therefore when administered, it may in fact cause polio." Id. at 18.

Based on this testimony regarding regulatory violations and causation, the trial court allowed the case to go to the jury, which returned an $8.5 million verdict against American Cyanamid in favor of Strong.

b. The company appealed, but the Court of Appeals, Eastern District, affirmed in relevant part.

The Court of Appeals held that Mr. Bozzo's testimony supported a finding that the company had committed a regulatory violation in failing to test the Sabin strains and intermediate materials. To begin with, the Court of Appeals concluded that the trial court was within its discretion when it allowed Mr. Bozzo to testify as an expert, following voir dire. Slip op. at 23-24. It also held, contrary to the company's argument, that interpreting regulations was not necessarily a matter of law for the court; experts could testify as to ultimate questions, like negligence. Id. at 24-26. In a footnote, the court of appeals assumed that, absent Mr. Bozzo's testimony, the question of interpretation would still have gone to the jury: "Had the trial court refused to allow Bozzo's testimony in this case, the jury would have been required to interpret highly technical neurovirulence regulations without any guidance." Id. at 26 n.5. Moreover, the Court of Appeals held that FDA's interpretation of the regulations was not controlling, because the agency was not a party to the case. Id. at 27. The Court of Appeals concluded: "We may agree that the FDA's interpretation of its regulations should be given

weight, but the standard of giving considerable deference to the agency interpretation does not apply where, as here, the only evidence of the FDA's interpretation of the polio vaccine regulations submitted to the jury occurred when Company read a portion of the preamble to the 1991 amendments during its cross-examination of Bozzo." Id.

The Court of Appeals also held that the plaintiff had introduced sufficient evidence of causation on one alleged regulatory violation (testing of original strains and intermediate materials) to allow the case to go to the jury. The company had cited three earlier cases involving Orimune for the proposition that, despite a regulatory violation, a plaintiff still must show that the violation caused the product to be more unsafe than it would have been in the absence of such a violation. Slip op. at 13. The Court of Appeals, however, distinguished those cases as involving no evidence of causation; it considered Mr. Bozzo's testimony about causation to be some evidence of causation, sufficient to present the matter to the jury. Id. at 13-20. The Court of Appeals also held that circumstantial, as opposed to expert, evidence could support a jury finding of causation. Id. at 20-22. Last, the Court of Appeals rejected the company's argument that Mr. Bozzo's testimony was insufficient because it had merely raised a possibility of causation. Id. at 22.

d. This Court granted American Cyanamid's application to transfer the case on December 18, 2007.

POINTS RELIED ON

I. The trial court erred in allowing a former federal agency official to testify about the meaning of federal regulations because interpreting regulations is a matter of law for the court, in that courts are required to give deference to the federal agency's interpretation of its own regulations.

Thomas Jefferson Univ. v. Shalala, 512 U.S. 504 (1994)

United States v. Cleveland Indians Baseball Co., 532 U.S. 200 (2001)

Auer v. Robbins, 519 U.S. 452 (1997)

United States v. Faltico, 687 F.2d 273 (8th Cir. 1982), cert. denied, 460 U.S. 1088 (1983)

II. The trial court erred in allowing the plaintiff's case to go to the jury because there was no evidence of causation, in that the plaintiff failed to offer expert testimony that a failure to perform neurovirulence testing on strain materials and intermediate materials actually increased the risk of harm to the plaintiff, when it is undisputed that such testing was performed on production seeds and monopools.

United States v. St. Louis Univ., 336 F.3d 294 (4th Cir.), cert. denied, 540 U.S. 1050 (2003)

American Cyanamid Co. v. St. Louis Univ., 336 F.3d 307 (4th Cir. 2003), cert. denied, 540 U.S. 1105 (2004)

Graham v. American Cyanamid Co., 350 F.3d 496 (6th Cir. 2003), cert. denied, 541 U.S. 990 (2004)

ARGUMENT

POINT I

THE TRIAL COURT ERRED IN ALLOWING A FORMER FEDERAL AGENCY OFFICIAL TO TESTIFY ABOUT THE MEANING OF FEDERAL REGULATIONS BECAUSE INTERPRETING REGULATIONS IS A MATTER OF LAW FOR THE COURT, IN THAT COURTS ARE REQUIRED TO GIVE DEFERENCE TO THE FEDERAL AGENCY'S INTERPRETATION OF ITS OWN REGULATIONS.

The trial court should have interpreted FDA regulations with deference to the agency's longstanding interpretation. In allowing the jury itself to interpret FDA regulations based on testimony of Mr. Bozzo, a former agency official, the trial court failed to give appropriate respect to federal law.

First, FDA regulations prohibit vaccine manufacturers from using "seed virus" to manufacture OPV unless that seed virus is first subjected to neurovirulence testing that satisfies certain standards. Under its longstanding interpretation of these regulations, FDA requires neurovirulence testing of production seeds and monopools, and not of earlier stages of production.

Second, the trial court had the responsibility to discern for itself the meaning of FDA's regulations, giving full deference to FDA's interpretation of its own regulations. The court erred in leaving the interpretation to the jury, based on testimony of a former FDA official that the regulations meant something different from what the agency itself said.

A. Under FDA's Longstanding Interpretation Of Its Regulations, "Seed Virus" Refers To "Production Seeds," Not To Materials At Earlier Stages Of Production.

The regulation in effect in 1987 required testing to determine whether the production seeds used in the manufacture of OPV were neurovirulent in monkeys:

> No seed virus shall be used for the manufacture of poliovirus vaccine unless its neurovirulence in Macaca monkeys is no greater than that of the Reference Attenuated Poliovirus distributed by the Bureau of Biologics Research and Review.

21 C.F.R. 630.10(b)(4) (1987 ed.) (emphasis added).[1] See also 21 C.F.R. 630.10(b)(5); 21 C.F.R. 630.16(b)(1). (The text of these regulations may be found in the Addendum to this brief.) "Neurovirulence is the capacity of an infectious agent to produce pathologic effects on the central nervous system. In this context, it refers to the vaccine's ability to cause paralytic poliomyelitis." Berkovitz v. United States, 486 U.S. 531, 543 n. 9 (1988).

Although FDA's regulations did not define "seed virus," FDA intended from the outset that section 630.10(b)(4) would cover testing of so-called production seeds, not intermediate materials, let alone original virus strains. The intent behind the regulation and FDA's interpretation of it was that if the production seeds and monopools, which are close to the final

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[1] When we cite these regulations, we refer to the 1987 version. Numerous changes were made in 1991, see generally 56 Fed. Reg. 21418 (May 8, 1991), some of them in response to tort litigation, see id. at 21421-23.

vaccine, are able to pass neurovirulence testing, it does not matter whether the "upstream" part of the production chain, which is more distant from the final vaccine, also passes it.

Our amicus brief here is not the first time FDA's intent has been stated. Its intent has been well understood not only by FDA but by the small number of companies manufacturing OPV. Historically, FDA worked informally with the small number of manufacturers of OPV to make clear how it interpreted its regulations. Hence, an official published interpretation or guidance generally was deemed unnecessary and was not available.

However, partly in response to litigation over the vaccine that took place in the 1980s, FDA took the opportunity presented by its amendment of some of its regulations in 1991 to put into writing several of its previous longstanding interpretations. In particular, FDA included the following statement in the preamble to its final rule in 1991, explaining that original strains did not have to undergo neurovirulence testing by the manufacturer:

> Because some lots manufactured in the early period of production of oral poliovirus vaccine were made directly from strain material, questions have been raised in litigation against the United States concerning testing such strain material. Litigants have argued that strain material used directly to produce vaccine lots should be tested in accordance with the requirements governing seed material. The agency continues to believe that the early use of strain material to produce vaccine lots directly did not thereby mean that the strain material had to be qualified as

> seed material. As previously stated, the agency believes that SO (produced by Dr. Sabin), SOM (produced by Merck, Sharp and Dohme), and SOR (produced by Pfizer, Ltd.) all constitute original Sabin strain material. Therefore, production of lots directly from any of these strain materials should not require that SO, SOM, or SOR be tested in accordance with the criteria for qualification of the seed virus in [21 C.F.R.] § 630.10(c).

56 Fed. Reg. 21418, 21422 (May 8, 1991) (emphasis added). The 1991 final rule revised the regulations, and section 630.10(b)(4) then read: "(4) If vaccine lots have been produced directly from strain materials (e.g., Sabin Original, Sabin Original Merck, or Sabin Original Rederived), the strain material is not required to be tested in accordance with the provisions of § 630.10(c)." 56 Fed. Reg. at 21432.

FDA's position against testing strain materials was accepted in the Sabin II decision. See In Re Sabin Oral Polio Vaccine Prods. Liab. Litig., 763 F. Supp. at 827 ("since Lederle itself did not produce the SOM [Sabin Original Merck virus strain] material and since the seeds and lots which were SOM's progeny were subject to neurovirulence testing, [FDA's predecessor] DBS's interpretation of the regulations was entirely proper").[2]

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[2] Similarly, in its Supreme Court brief in Berkovitz, supra, the government distinguished between the strain and the seed virus, the latter of which had to be tested:

> The Sabin strain is not produced by the manufacturer. Rather,

(continued...)

Mr. Bozzo's testimony that neurovirulence testing is required on strain materials also does not reflect practical realities. As Dr. Sabin himself indicated, he produced only 10 milliliters of Type III original strain. See Sabin & Boulger, "History of Sabin Attenuated Poliovirus Oral Live Vaccine Strains," 1 J. Biol. Standardization 115, 117 (1973). But in order to test for neurovirulence under FDA regulations, a manufacturer must use, at an absolute minimum, over 81 milliliters to inoculate laboratory monkeys. See 21 C.F.R. 630.10(b)(4); 21 C.F.R. 630.16(b)(1). Conducting neurovirulence testing alone on the Type III original strain materials would have used up the entire world supply of those irreplaceable materials. And the regulations require other types of testing, as well.

As for the intermediate materials, it is FDA's longstanding interpretation that those intermediate materials (which come between strain materials and production seeds) also do not have to be tested. As with its interpretation regarding strain materials, this is not the first

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[2](...continued)

> it is obtained directly from Dr. Sabin. [¶] Once the manufacturer obtains the original virus strain from Dr. Sabin, it grows a seed virus from that strain. * * * [M]anufacturers are simply forbidden by the regulations to use any seed virus without first performing certain prescribed tests to ensure that the neurovirulence of the seed virus "is no greater than that of the * * * Reference Attenuated Poliovirus" distributed by the agency.

Brief for the United States, Berkovitz, supra, 1988 WL 1026265, at *32 (March 29, 1988).

time FDA has stated its interpretation of the regulations. FDA has previously expressed this interpretation in public on several occasions. For example, during a 1991 deposition in the In Re Sabin litigation, attended by Stanley Kops, co-counsel for Mr. Strong in the current litigation, Dr. Bennett Elisberg, a former official from the Bureau of Biologics (the predecessor of the current FDA agency known as the Center for Biologics Evaluation and Research), offered the following testimony when asked about the testing that was required to be performed on certain seeds that were used to produce vaccine monopools:

> Q. If seeds had to be tested, did Lederle or the government have to test [production seed] 45B85 before it was used to make monopools?
>
> * * *
>
> A. The manufacturer would be required to test the seed, to establish its acceptability.
>
> Q. Would that apply not only to that seed which we might call a production seed but to the master seed from which it was derived?
>
> A. Only production seed.

Deposition of Dr. Bennett Elisberg (Jan. 31, 1991) at 886.

When the questioning continued, Dr. Elisberg reiterated FDA's interpretation:

> Q. Tell me where it says production seed and not master seeds?

A. These are old regulations.

Q. Those are the 73 but the provision has not changed in the 630 series. I draw your attention to 73.116B3 and 4.

A. It says here the title, the title for the appropriate section, that is 73.110B.

Q. Right.

A. Criteria for acceptable strains and acceptable seed virus.

Q. Right.

A. And then it says here under B, it is four and says "no seed virus shall be used for the manufacture of polio virus vaccine" and then it identifies the tests that are being done. That refers to the production seed.

Q. Where does it say that?

A. What else can you use for the manufacture of polio virus vaccine other than a production seed?

Q. Before you get to the production seed, you have to have something that gives birth to it, you have to have a master seed and above that a strain in the genealogy table, right?

* * *

A. The interpretation that we have placed on this section refers to production seeds.

Q. Only?

A. Yes.

Id. at 887-88.

FDA's interpretation that "seed virus" means production seeds remains the same today. It was recently reiterated by an FDA witness in a 2006 deposition conducted by Mr. Kops himself in Gannon v. United States, 2007 WL 2071878 (E.D. Pa. July 17, 2007), appeal pending, No. 07-3428 (3d Cir.), a Federal Tort Claims Act case concerning OPV:

Q. So, you are saying that if it is a harvest for another seed you don't have to do the test, but if it produces a harvest that ends up being a monovalent [pool], you have to do the test?

A. Right.

Deposition of Ronald Lundquist (Aug. 29, 2006) at 259.

Last, the government's 1988 Supreme Court brief in Berkovitz stated: "The seed virus is in turn used to produce the monopools from which portions are combined to make up the actual vaccine ingested by the public." Brief for the United States, Berkovitz, supra, 1988 WL 1026265, at *32 (March 29, 1988). This, too, reflected FDA's interpretation that the "seed virus" that the regulations require to be tested is the step directly above monopools in the production chain – that is, that the "seed virus" means the production seeds.

In short, FDA's longstanding interpretation of these regulations, continuing today, is that "seed virus" refers to production seed, and not to strains or intermediate materials.

B. The Trial Court Had the Responsibility To Discern For Itself The Meaning Of FDA's Regulations, Giving Full Deference To FDA's Interpretation Of Its Own Regulations.

The trial court erred in allowing Mr. Bozzo, a former FDA official, to offer his personal interpretation of FDA's regulations contradicting the agency's longstanding interpretation. The trial court should have interpreted the regulations itself and given guidance to the jury, with all appropriate deference to FDA's interpretation. It should not have allowed the jury to interpret the regulations independently.

1. It is well established that a federal agency's interpretation of its own regulations is entitled to deference. Thomas Jefferson Univ. v. Shalala, 512 U.S. 504, 512 (1994) ("the agency's interpretation must be given controlling weight unless it is plainly erroneous or inconsistent with the regulation") (internal quotation marks omitted); see also United States v. Cleveland Indians Baseball Co., 532 U.S. 200, 219 (2001) ("[T]he Rulings simply reflect the agency's longstanding interpretation of its own regulations. Because that interpretation is reasonable, it attracts substantial judicial deference."); Ballenger v. Johanns, 495 F.3d 866, 872 (8th Cir. 2007) ("we must defer to the agency's interpretation of its own regulation").

Contrary to the view of the Court of Appeals, slip op. at 27 (distinguishing Thomas Jefferson Univ. on the ground that "FDA is not a party to this case"), deference is appropriate even if the agency is not a party to the case; indeed, deference is appropriate even if the first time the agency has expressed its interpretation of the regulation is in its amicus brief, Auer v. Robbins, 519 U.S. 452, 462 (1997) (interpretation in amicus brief was not post hoc

rationalization and there was "no reason to suspect that the interpretation does not reflect the agency's fair and considered judgment on the matter in question"), at least if "the language of the regulation is ambiguous." Christensen v. Harris County, 529 U.S. 576, 588 (1999). See also M. Fortunoff of Westbury Corp. v. Peerless Ins. Co., 432 F.3d 127, 139 (2d Cir. 2005) ("To the extent that the amicus brief is interpreting the agency's own regulations, as it is here, it is entitled to deference under Auer, * * * as long as the regulation is ambiguous – which we have observed it is."); Oregon Paralyzed Veterans v. Regal Cinemas, Inc., 339 F.3d 1126, 1131 n.6 (9th Cir. 2003), cert. denied, 542 U.S. 937 (2004) ("Insofar as the district court suggested that an agency interpretation first advanced in an amicus brief is somehow less valid or less entitled to deference than one promulgated elsewhere, this is a position without legal support.").

Similar principles apply to state regulations in the Missouri courts.[3] Ultimately, however, this Court should apply federal principles of deference when the question is the interpretation of a federal agency of its own federal regulation issued pursuant to a federal statute. See, e.g., Citibank (South Dakota), N.A. v. Mincks, 135 S.W.3d 545, 559 (Mo. Ct. App. S.D. 2004) ("we believe the Federal Reserve Board's interpretation of the Truth-in-Lending-Act and its implementing regulations are entitled to substantial deference as we analyze the issues presented in Citibank's appeal"); Prince v. Division of Family Servs., 886

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[3] E.g., State ex rel. Webster v. Missouri Resource Recovery, Inc., 825 S.W.2d 916, 931 (Mo. App. S.D. 1992) ("Deference to the agency action is even more clearly in order when interpretation of its own regulation is at issue.").

S.W.2d 68, 72 (Mo. Ct. App. W.D. 1994) ("When interpreting agency regulations, if the intent of Congress is clear, there is no further interpretation needed; if not clear then this court is to defer to a reasonable agency interpretation.") (relying on U.S. Supreme Court's Chevron doctrine).[4]

2. The trial court erred in allowing Mr. Bozzo, a former FDA official, to testify about his opinion of the meaning of the regulations, and the Court of Appeals erred in upholding that decision.[5]

First, the interpretation of a regulation is question of law; it is precisely the type of legal question that courts generally are expected to address. See, e.g., United States v. Faltico, 687 F.2d 273, 276 (8th Cir. 1982), cert. denied, 460 U.S. 1088 (1983) (upholding trial court's refusal to allow testimony interpreting regulations, because "any questions of law are determined exclusively by the court"); see also Williams v. Department of Building

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[4] Similarly, a state court's interpretation of a federal statute also involves federal interpretive principles: "At the outset we note that Congressional intent is the guidepost to judicial interpretation of federal statutes." Kidd v. Pritzel, 821 S.W.2d 566, 568 (Mo. Ct. App. W.D. 1991).

[5] Although we agree with American Cyanamid that Mr. Bozzo's former position at FDA did not qualify him to interpret the regulations, our position here does not turn on the qualifications of the particular former official. It is our position that a court must defer to the federal agency's own interpretation, as expressed in recognized sources, regardless of the level of knowledge of an individual former official who testifies to the contrary.

Devel. Servs., 192 S.W.3d 545, 547 (Mo. Ct. App. S.D. 2006) ("the interpretation of a city ordinance is a question of law"); Richard v. Missouri Dept. of Corrections, 162 S.W.3d 35, 37 (Mo. Ct. App. W.D. 2005) ("The interpretation of a statute is a question of law."); HHC Medical Group, P.C. v. City of Creve Coeur Bd. of Adjustment, 99 S.W.3d 68, 71 (Mo. Ct. App. E.D. 2003) ("The interpretation of an ordinance is a question of law."). It follows that a court errs when it abdicates its judicial function by handing the matter off to a jury of laymen. White v. Reitz, 129 Mo. App. 307, 108 S.W. 601, 603 (1908) ("[I]t was not proper to leave it to the jury to interpret those sections [of the code] and apply them to the facts in the case as was done by the instruction. It was the duty of the court to have interpreted the sections read in evidence to the jury.").

Second, by allowing the jury to decide the meaning of FDA's regulation after hearing testimony, the trial court failed to give FDA's own interpretation of its regulation the deference that it is due. To be sure, the trial court did not have before it the deposition testimony of FDA employees we quoted above, which set forth the agency's interpretation. However, it did have before it the 1991 preamble to FDA's rulemaking, and based on that source alone, even without regard to the principles discussed immediately above, the court should have given deference to the agency's interpretation. Since it was clear that Mr. Bozzo's testimony conflicted with FDA's official interpretation of its regulation, the court should not have allowed the jury to decide between the two. In suggesting that the jury had to hear Mr. Bozzo's testimony or else it "would have been required to interpret highly technical neurovirulence regulations without any guidance," slip op. at 26 n.5, the Court of Appeals

erroneously assumed that the trial court did not itself have the responsibility to interpret the regulations and to give guidance when it instructed the jury.

Third, allowing the jury to decide the meaning of federal regulations puts parties who fail to offer testimony from federal officials at a severe disadvantage. See Slip op. at 28 (jury's reliance on Mr. Bozzo's testimony was reasonable, because "Company presented no witnesses from the agency"). In penalizing the company for failing to present agency witnesses, the Court of Appeals failed to take into account that FDA officials are not at a private litigant's beck and call to testify about the meaning of FDA regulations. Indeed, FDA's "Touhy" regulations, see United States ex rel. Touhy v. Ragen, 340 U.S. 462 (1951), severely restrict testimony by FDA officials or employees. The general rule is that no FDA officer or employee may give testimony in any tribunal regarding FDA functions or information acquired in the discharge of official duties. 21 C.F.R. 20.1(a). Furthermore, if any officer or employee is subpoenaed to testify, that officer or employee must, under the regulations, appear and "respectfully decline to testify on the grounds that it is prohibited by" the regulations, unless the testimony is otherwise authorized by FDA's Commissioner. 21 C.F.R. 20.1(b). However, the regulations do provide a "person who desires testimony from any employee" with the opportunity to make a formal request, "verified by oath, directed to the Commissioner setting forth his interest in the matter sought to be disclosed and designating the use to which such testimony will be put in the event of compliance with such request." 21 C.F.R. 20.1(c). Then, "[i]f it is determined by the Commissioner, or any other officer or employee of the Food and Drug Administration whom he may designate to act on his behalf

for the purpose, that such testimony will be in the public interest and will promote the objectives of the act and the agency, the request may be granted." Id.

In short, the trial court failed to do its judicial duty when it left the interpretation of FDA's regulations to the jury, and the Court of Appeals improperly gave its blessing to the trial court's error.

POINT II

THE TRIAL COURT ERRED IN ALLOWING THE PLAINTIFF'S CASE TO GO TO THE JURY BECAUSE THERE WAS NO EVIDENCE OF CAUSATION, IN THAT THE PLAINTIFF FAILED TO OFFER EXPERT TESTIMONY THAT A FAILURE TO PERFORM NEURO-VIRULENCE TESTING ON STRAIN MATERIALS AND INTER-MEDIATE MATERIALS ACTUALLY INCREASED THE RISK OF HARM TO THE PLAINTIFF, WHEN IT IS UNDISPUTED THAT SUCH TESTING WAS PERFORMED ON PRODUCTION SEEDS AND MONOPOOLS.

The United States agrees with American Cyanamid's argument that there was insufficient evidence of causation to support the jury verdict. The trial court should not have allowed speculative testimony about causation to be offered by a former FDA official.

In a case like this, involving a vaccine that has inherent risks of adverse effects in rare cases, a plaintiff who suffers such adverse effects cannot prove causation unless he shows, through expert testimony, that the conduct of the defendant regarding the vaccine admin-

istered to him increased those inherent risks. Three federal court of appeals decisions have so held in cases involving claims of injury from OPV. In United States v. St. Louis Univ., 336 F.3d 294 (4th Cir.), cert. denied, 540 U.S. 1050 (2003) (applying Missouri law), the court held that the plaintiff had to prove through expert testimony that he likely would not have contracted polio from a vaccine that had met regulatory requirements:

> As to proximate cause, we note that all OPV, including OPV that satisfied all regulatory requirements, carried the risk that the recipient would actually contract polio. Therefore, to show that Danny's polio was caused by the government's regulatory violations, we conclude that SLU was required to establish that Danny likely would not have contacted polio (or would have contracted a less severe case of polio) from a vaccine that satisfied the government's neurovirulence requirements. Any lesser standard would result in the government being held strictly liable for its regulatory violations, which would be inconsistent with Missouri law. And this evidence, of course, must be in the form of expert testimony.

Id. at 303 (citation omitted). See also American Cyanamid Co. v. St. Louis Univ., 336 F.3d 307, 310 (4th Cir. 2003), cert. denied, 540 U.S. 1105 (2004) (applying Missouri law) ("SLU presented no expert testimony showing that Danny Callahan would not have contracted polio or would have contracted a less severe case of polio had he been given a vaccine complying

with the neurovirulence regulations."); accord, Graham, 350 F.3d at 510 (Ohio law) ("plaintiffs have not established that this alleged regulatory noncompliance increased the risk that the Orimune vaccine would cause polio in recipients or those in close contact with recipients").

We agree with American Cyanamid that this rule about causation is highly significant, because the possibility of reversion to virulence increases with each tissue culture passage of the strain material, and we also agree that the company did test the later stages of production – production seeds and monopools – for neurovirulence. Indeed, as the company stated in its application to this Court: "If tests on the downstream materials were satisfactory (and they indisputably were here), then the upstream materials had to have been *at least as safe*." Application, at 11. That is, even if the Sabin strain materials and the intermediate seeds had been tested, there would have been no difference in the neurovirulence of the final product, because the production seeds and monopools themselves were tested down the production line. At trial, Mr. Bozzo disclaimed any opinion about whether the actual vaccine administered to Strong was safe or unsafe; he merely testified that, generally speaking, when testing is not done, it makes it possible that a product is unsafe.[6]

Because there was no evidence that any failure to test the strain materials or intermediate materials increased the risk already inherent in the vaccine, the Court of Appeals erred in allowing the jury verdict to stand.

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[6] Mr. Bozzo testified that it could possibly have had an effect on safety: "Well, if you omit safety tests, then you raise the possibility of a product being unsafe." Id. at 17.

CONCLUSION

For the foregoing reasons, the Court should grant judgment in favor of American Cyanamid notwithstanding the verdict or, in the alternative, order a new trial.

Respectfully submitted,

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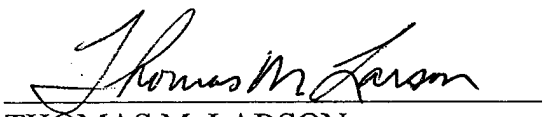

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CERTIFICATE OF SERVICE

I hereby certify that on this 5th day of February 2008, I served the foregoing "Brief for the United States as Amicus Curiae," by causing two hard copies of the brief and one electronic copy on CD to be sent by Federal Express, for overnight delivery, to each of the following:

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ADDENDUM – 1987 FDA Regulations

21 C.F.R. 630.10(b)(4)

No seed virus shall be used for the manufacture of poliovirus vaccine unless its neurovirulence in Macaca monkeys is no greater than that of the Reference Attenuated Poliovirus distributed by the Bureau of Biologics Research and Review. The neurovirulence of the seed virus shall be demonstrated by the following tests to be performed by the manufacturer: (i) The test prescribed in § 630.16(b)(1) using seed virus as test material in place of monovalent virus pool material and (ii) the following comparative intramuscular neurovirulence test: Each of at least 10 monkeys shall be injected with a total of 5.0 ml. of the seed virus under test in one or more proximate locations of either a gluteus or gastrocnemius muscle. Similar injections shall be made in another group of 10 monkeys using the Reference Attenuated Poliovirus. Each monkey shall be injected intramuscularly with no less than 10 TCID T25 T20 of viral inoculum. All monkeys shall be observed for 17 to 21 days and a comparative evaluation shall be made of the evidence of neurovirulence of the virus under test and the Reference Attenuated Poliovirus, as prescribed in § 630.16(b)(1)(iii).

21 C.F.R. 630.10(b)(5)

Subsequent and identical neurovirulence tests shall be performed in monkeys whenever there is evidence of a change in the neurovirulence of the production virus, upon introduction of a new production seed lot, and as often as necessary otherwise to establish to the satisfaction of the Director, Office Biologics Research and Review that the seed virus strains for vaccine manufacture have maintained their neurovirulence properties as set forth in § 630.16(b)(1)(iii).

21 C.F.R. 630.16(b)(1)

(b)(1)(i) Intrathalamic inoculation Each of at least 30 monkeys shall be injected intracerebrally by placing 0.5 ml. of virus pool material into the thalamic region of each hemisphere. Comparative evaluations shall be made with the virus pool under test and the Reference Attenuated Poliovirus. Only monkeys that show evidence of inoculation into the thalamus shall be considered as having been injected satisfactorily. If on examination there is evidence of failure to inoculate virus pool material into the thalmus, additional monkeys may be inoculated in order to reestablish the minimum number of 30 monkeys for the test.

(b)(1)(ii) Intraspinal inoculation Each of a group of at least five monkeys shall be injected intraspinally with 0.2 ml. of virus pool material containing at least 10 TCID T25 T20 per ml. and each monkey in additional groups of at least five monkeys shall be injected intraspinally with 0.2 ml of a 1:1,000 and 1:10,000 dilution respectively, of the same virus pool material. Comparative evaluations shall be made with the virus pool under test and the reference material. Only monkeys that show microscopic evidence of inoculation into the gray matter of the lumbar cord shall be considered as having been injected satisfactorily. If on examination there is evidence of failure to inoculate intraspinally, additional animals may be inoculated in order to reestablish the minimum number of five animals per group.

(b)(1)(iii) Determination of neurovirulence At the conclusion of the observation period comparative histopathological examinations shall be made of the lumbar cord, cervical cord, lower medulla, upper medulla, mesencephalon and motor cortex of each monkey in the groups injected with virus under test and those injected with the Reference Attenuated Poliovirus, except that for

animals dying during the test period, these examinations shall be made immediately after death. If at least 60 percent of the animals of a group survive 48 hours after inoculation, those animals which did not survive may be replaced by an equal number of animals tested as prescribed in paragraph (b)(1) of this section. If less than 60 percent of the animals of a group survive 48 hours after inoculation, the test must be repeated. At the conclusion of the observation the animals shall be examined to ascertain whether the distribution and histological nature of the lesions are characteristics of poliovirus infection. A comparative evaluation shall be made of the evidence of neurovirulence of the virus under test and the Reference Attenuated Poliovirus with respect to (a) the number of animals showing lesions characteristic of poliovirus infection, (b) the number of animals showing lesions other than those characteristic of poliovirus infection, (c) the severity of the lesions, (d) the degree of dissemination of the lesions, and (e) the rate of occurrence of paralysis not attributable to the mechanical injury resulting from inoculation trauma. The virus pool under test is satisfactory for poliovirus vaccine only if at least 80 percent of the animals in each group survive the observation period and if a comparative analysis of the test results demonstrate that the neurovirulence of the test virus pool does not exceed that of the Reference Attenuated Poliovirus.

(b)(1)(iv) Test with Reference Attenuated Poliovirus The Reference Attenuated Poliovirus shall be tested as prescribed in paragraph (b)(1)(i) and (ii) of this section at least once for every 10 production lots of vaccine, except that the interval between the test of the reference and the test of any lot of vaccine shall not be greater than 3 months. The test procedure shall be considered acceptable only if lesions of poliomyelitis are seen in monkeys inoculated with the reference material at a frequency statistically compatible with all previous tests with this preparation.