UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF FLORIDA
FT. MYERS DIVISION

DR. AND MRS. ROBERT SHARKEY
on behalf of RYAN REED SHARKEY,
a minor,

Plaintiffs,

v. Civil Action No. 2:04-CV-552

FOOD AND DRUG ADMINISTRATION,

Defendant,

and

MERCK & CO., INC.,

Defendant-Intervenor.
_____/

MEMORANDUM IN OPPOSITION TO DEFENDANTS' MOTIONS FOR SUMMARY JUDGMENT AND IN SUPPORT OF PLAINTIFFS' MOTION FOR SUMMARY JUDGMENT OR FOR DISCOVERY

Plaintiffs brought this action under the Freedom of Information Act (FOIA), 5 U.S.C. § 552, to compel the Food and Drug Administration (FDA) to produce records reflecting the net number of doses in each lot of hepatitis B vaccine distributed in the United States. The FDA has identified 19 documents responsive to plaintiffs' request but has refused to produce the records on the ground that they contain confidential commercial information subject to withholding under FOIA Exemption 4, 5 U.S.C. § 552(b)(4). The FDA and defendant-intervenor Merck & Co., Inc. (Merck) have filed motions for summary judgment, and plaintiffs have filed a cross-motion for summary judgment or, in the alternative, for discovery. Because defendants have failed to meet their burden of demonstrating that the requested documents are exempt from disclosure, the Court should deny defendants' motions for summary judgment, grant summary judgment for plaintiffs, and order the FDA to produce the requested records.

FACTS

There are two recombinant hepatitis B vaccines licensed for use in the United States: Merck's Recombivax HB and Glaxo's Engerix-B.[1] On March 10, 2003, plaintiffs submitted a FOIA request to the FDA seeking the net number of doses (doses distributed less doses returned) in each lot of recombinant hepatitis B vaccine distributed in the United States. Plaintiffs seek this information to assist their son's physicians in determining whether an adverse reaction to the hepatitis B vaccine was the cause of his severe injuries. Complaint ¶ 4. Releasing this information would also aid research on vaccine safety and respond to the calls of those concerned with vaccine safety to provide greater understanding of vaccine adverse reaction data.

In fact, the National Network for Immunization Information, a coalition including the Infectious Diseases Society of America, the American Academy of Pediatrics, and the American Academy of Family Physicians has taken the position that this information should be released and would have no negative competitive impact on the manufacturers. In a publication of October of 2000, the organization stated:

> The perspective of the National Network for Immunization Information is that vaccine manufacturers should release to the public information on the number of doses created and used. Releasing this information to the public, or allowing the FDA to do so, will have an important benefit and is unlikely to put any vaccine manufacturer at a competitive disadvantage in the marketplace.

National Network for Immunization Information, "Common Questions About Adverse Events that Follow Vaccination" (2000), attached hereto as Exhibit "A."

The FDA has identified 19 documents responsive to plaintiffs' request. The documents contain information submitted to the FDA by the two manufacturers pursuant to 21 C.F.R. § 600.81 and predecessor regulations. The FDA has withheld the documents because it claims that the records contain confidential commercial information the release of which could cause

[1]Engerix-B is manufactured by GlaxoSmithKline Biologicals, SA, and distributed in the United States by SmithKline Beecham Corporation d/b/a GlaxoSmithKline. Thomas Decl. ¶ 2-3. Plaintiffs will refer to these companies as "Glaxo."

competitive harm to the two vaccine manufacturers. As factual support for this assertion, the FDA and Merck rely solely on paragraphs 27 and 28 of the Ryan Declaration, paragraphs 5 and 6 of the Thomas Declaration, and paragraphs 3-6 of the Turner declaration.

Paragraphs 3 and 4 of the Turner Declaration and paragraph 6 of the Thomas Declaration assert that the manufacturers treat the net number of doses as confidential information and want to keep it that way— facts that plaintiffs cannot dispute at present. The remaining assertions on which defendants base their case are:

1) Release of the withheld information could provide insight into the two manufacturers' respective production capacities (Ryan Decl. ¶ 27, Thomas Decl. ¶ 5, Turner Decl. ¶ 5);
2) Release of the withheld information could provide insight into the two manufacturers' respective marketing capabilities, giving insight into market share and sales volume for specific time periods (Ryan Decl. ¶¶ 27-28, Thomas Decl. ¶ 5); and
3) Such insights could cause competitive harm. (Thomas Decl. ¶ 5, Turner Decl. ¶ 6).

As discussed in detail below, these assertions are conclusory and thus insufficient to establish the applicability of FOIA Exemption 4. Moreover, plaintiffs have submitted an affidavit from Donald H. Marks, M.D. Ph.D., an expert in the field of vaccine development and production, that disputes defendants' claim that release of the net number of doses per lot of hepatitis B vaccine could cause competitive injury by revealing to each manufacturer otherwise unknown information about the other's production process and marketing schemes. Specifically, Dr. Marks states that the net number of doses per lot would give no insight into each company's manufacturing process, the product distribution plan, or the marketing of the vaccine, as they are unrelated. The affidavit of Dr. Marks is attached hereto as Exhibit "B."

ARGUMENT

Plaintiffs do not challenge the adequacy of FDA's search for responsive documents. Thus, the only issue in this case is whether the 19 documents identified by FDA as responsive to

plaintiffs' FOIA request contain confidential commercial information such that they may be withheld in full under FOIA Exemption 4. If not, plaintiffs are entitled to summary judgment because it is undisputed that plaintiffs made a valid FOIA request, the FDA has responsive documents, and the FDA has not released the requested information.

I. Defendants Have the Burden of Demonstrating That the Requested Information Is Exempt from Disclosure.

FOIA provides an expansive right for citizens to obtain information from the federal government. *See* 5 U.S.C. § 552; *Ely v. FBI*, 781 F.2d 1487, 1489 (11th Cir. 1986). Disclosure of information held by government agencies is mandatory unless the information is subject to one of the limited exceptions provided in 5 U.S.C. § 552(b). These exceptions are to be construed narrowly. *Dep't of the Air Force v. Rose*, 425 U.S. 352, 361 (1976). Efforts by the government to invoke a FOIA exception must be reviewed in an exacting manner by the courts: "The burden is squarely on the government to prove that the information in question is covered by one of the exemptions." *Ely*, 781 F.2d at 1489-90. The court should give no deference to the agency's reasoning for withholding the information and must decide *de novo* whether the exception applies. 5 U.S.C. § 552(a)(4)(B); *see also Mead Data Cent., Inc. v. U.S. Dep't of the Air Force*, 566 F.2d 242, 251 (D.C. Cir. 1977) ("[T]he agency's opinions carry no more weight than those of any other litigant in an adversarial contest before a court."). Nor should the court defer to agency regulations on withholding information. *See Ass'n of Retired R.R. Workers v. U.S. R.R. Retirement Bd.*, 830 F.2d 331, 333-34 (D.C. Cir 1987); *Public Citizen Health Research Group v. FDA*, 704 F.2d 1280, 1287 (D.C. Cir. 1983). Ultimately, "[t]he trial court *must* find an adequate factual basis to support a finding of privilege." *Cappabianca v. Comm'r*, 847 F. Supp. 1558, 1562 (M.D. Fla. 1994).

FOIA Exemption 4 allows the government to withhold "commercial or financial information obtained from a person [that is] privileged or confidential." 5 U.S.C. § 552(b)(4).[2]

[2]Although Exemption 4 also applies to "trade secrets," this term is construed narrowly as "a secret, commercially valuable plan, formula, process, or device that is used for the making, preparing, compounding, or processing of trade commodities and that can be said to be the end

When the government obtains information from someone who is legally required to submit that information, that information is considered confidential under the statute if its disclosure would "cause substantial harm to the competitive position of the person from whom the information was obtained." *Nat'l Parks & Conservation Ass'n v. Morton (Nat'l Parks I),* 498 F.2d 765, 770 (D.C. Cir. 1974); *see also Westchester Gen. Hosp., Inc. v. Dep't of Heath, Educ., & Welfare,* 464 F. Supp. 236, 245 (M.D. Fla. 1979).[3] In turn, this showing of harm requires the withholding agency to meet its burden on two questions: "In order to show a likelihood of substantial competitive harm, the agency must show (i) that the entity that will suffer harm is in actual competition, and (ii) that substantial competitive injury will result from disclosure." *Miami Herald Publ'g Co. v. U.S. Small Bus. Admin.,* 670 F.2d 610, 613-14 (5th Cir. Unit B 1982) (citing *Gulf & W. Indus., Inc., v. United States,* 615 F.2d 527, 530 (D.C.Cir.1979); *Nat'l Parks & Conservation Ass'n v. Kleppe (Nat'l Parks II),* 547 F.2d 673, 679 (D.C.Cir.1976)).

The government must prove the elements of "substantial competitive harm" through concrete evidence, because "conclusory and generalized allegations of substantial competitive harm . . . are unacceptable and cannot support an agency's decision to withhold requested documents." *Public Citizen,* 704 F.2d at 1291; *see also Niagara Mohawk Power Corp. v. U.S. Dep't of Energy,* 169 F.3d 16, 18 (D.C. Cir. 1999)(noting that "the agency has the burden of showing that requested information comes within a FOIA exemption" and that "we have more than once held that such conclusory and generalized assertions are not enough" to meet the

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product of either innovation or substantial effort." *Public Citizen,* 704 F.2d at 1288; *see also Burnside-Ott Aviation Training Ctr., Inc. v. United States,* 617 F. Supp. 279, 285 (S.D. Fla. 1985) (adopting *Public Citizen* standard to define "trade secret"). The government has correctly conceded that the information sought by plaintiff does not constitute a "trade secret" within the meaning of Exemption 4. Gov. Memo. 12 n.1.

[3]Although the D.C. Circuit subsequently clarified that for *voluntary* submissions the government need not demonstrate substantial competitive harm to claim Exemption 4, it simultaneously affirmed the *National Parks* standard for *mandatory* submissions. *See Critical Mass Energy Project v. Nuclear Regulatory Comm'n,* 975 F.2d 871, 879 (D.C. Cir. 1992) (en banc).

burden); *Miami Herald*, 670 F.2d at 614 n.9 (describing conclusory evidence as inadequate to carry the government's Exemption 4 burden).

II. Defendants Have Failed to Establish That Disclosure of the Requested Information Would Cause Substantial Harm to the Competitive Positions of the Two Manufacturers.

A. Defendants have not shown that the two manufacturers of hepatitis B vaccine are in actual competition.

Defendants have failed to provide sufficient evidence to establish that Glaxo and Merck are in "actual competition" with regard to hepatitis B vaccine. *See Miami Herald*, 670 F.2d at 614. The Ryan and Thomas declarations do not claim that there is actual competition in the hepatitis B vaccine market, and the Turner declaration states only that the FDA has licensed two manufacturers to produce hepatitis B vaccine and that "[c]ompetition involving this product, therefore, is especially keen." ¶6. This statement is entirely conclusory, and therefore does not provide evidence sufficient to meet the government's burden. *See Public Citizen*, 704 F.2d at 1291; *Miami Herald*, 670 F.2d at 614 n.9. The fact that there are two licensees for a particular vaccine certainly does not prove that the market for that vaccine is competitive. Indeed, Merck and Glaxo have entered into a joint agreement licensing the technology behind the hepatitis B vaccine from its patent holder. *See In the Matter of the Arbitration Between Smithkline Beecham Biologicals, S.A. v. Biogen, Inc.*, No. 95 Civ. 4988 (JGK), 1996 WL 209897, at *1 (S.D.N.Y. Apr. 26, 1996). The existence of this cooperative relationship undermines the unsupported assertion that competition between Merck and Glaxo in the hepatitis B vaccine market "is especially keen." Turner Decl. ¶ 6.

Defendants attempt to bolster their claim that there is competition by citing *Public Citizen Health Research Group v. NIH*, 209 F. Supp. 2d 37 (D.D.C. 2002), but that case does not speak to the characteristics of this particular vaccine market. In *Public Citizen*, the plaintiff requested documents on the royalty rates that the National Institutes of Health was paid for its cooperative licensing agreements with nearly 500 pharmaceutical companies in many different

product areas. *See id*. at 40-41. Required to consider the pharmaceutical industry as a whole, the court determined that competition exists within the broad industry. *See id*. at 47. That conclusion is inapposite here: That there is competition within the pharmaceutical industry as a whole does not mean there is competition within the hepatitis B vaccine market, the one small component of the industry relevant to this case. *See also* Food and Drug Administration Public Information, 39 Fed. Reg. 44,602, 44,641 (Dec. 24, 1974) (explaining that certain information in FDA's vaccine licensing file would not be withheld from public disclosure even though it would be withheld for other types of drugs since regulatory scheme and competitive considerations differ between vaccines and other drugs).

Even if defendants had offered more than a single conclusory statement as support for their claim of actual competition, the claim would be entitled to no weight because the vaccine market is structured in such a way that there is very limited competition. *See Niagara Mohawk*, 169 F.3d at 18-19 (denying government's motion for summary judgment on Exemption 4 where requester alleged that structure of electricity market eliminated genuine competition). A market's theoretically competitive nature is not enough to overcome a lack of competition based on the realities of the marketplace: "[The government's] other arguments relating to competitive injury are legally inadequate . . . . For example, [the government] argues that the [companies] may face future or potential competition. But the test explicitly requires proof that the submitters face *actual* competition." *Id.* at 19 (citing *Nat'l Parks II*, 547 F.2d at 679). Recent scholarship examining the American vaccine market has found that it is not competitive. For example, a just-published study in *Health Affairs*, a leading journal in the health policy field, found:

> [G]iven the cost and demand conditions of most vaccine markets, long-term equilibrium is likely to be one supplier or at most a few suppliers of each vaccine type at any point in time…. [I]t is unrealistic to anticipate investment in new 'me-too' forms of old vaccines…. [P]otential entrants have little incentive to invest in developing similar products since they could not hope to recoup their R&D costs unless they have a sufficiently superior product to command a higher price or capture a dominant market share…. By contrast, a single-supplier

> equilibrium is less frequently the norm in pharmaceutical markets because those markets are generally larger relative to fixed costs; differentiated products can coexist because they often differ in safety or efficacy for major groups of consumers; demand is less concentrated; and there are no government recommendations that steer utilization toward the single preferred product.

Patricia Danzon & Nuno Sousa Pereira, *Why Sole-Supplier Vaccine Markets May Be Here To Stay*, *Health Affairs*, May/June 2005, at 694-95, attached hereto as Exhibit "C."[4] The defendants make no effort to prove—nor do they even claim—that they face any prospect of new entrants into the hepatitis B vaccine market.

B. Defendants have failed to establish that disclosure of the requested information will result in substantial competitive injury.

Even if defendants had shown that the two hepatitis B vaccine manufacturers are in actual competition, the government's Exemption 4 claim would fail because defendants have not shown that "substantial competitive injury will result from disclosure" of the requested information. *Miami Herald*, 670 F.2d at 613-14. Defendants claim that release of the requested records could cause competitive harm by providing each manufacturer insight into the other's market capabilities and production process and capacities. *See* Ryan Decl. ¶¶ 27-28, Thomas Decl. ¶ 5, Turner Decl.¶¶ 5-6. But, defendants rely on conclusory declarations that offer too little explanation to support the government's Exemption 4 burden, *see Public Citizen*, 704 F.2d at 1291, and their conclusions are in dispute.

1. To the extent that the requested records may reveal market share information, disclosure of the data will not cause competitive harm because the two manufacturers already have access to market share data.

Defendants' claim with respect to market share information is particularly specious. There are only two manufacturers of hepatitis B vaccine and the FDA concedes that the total net

[4]The Washington Post has described the articles in Health Affairs as "rigorously researched." *Readings*, *Wash. Post*, Jan. 11, 2004, at F3.

number of doses distributed has been published. FDA Memo. 16-17, n.3. Although the FDA argues that the published report does not provide distribution data by specific hepatitis B vaccine manufacturer, both manufacturers can reconstruct this information by comparing the combined total for the two manufacturers with their individual company records. Thus, contrary to the government's assertion that the release of the aggregate data does not undercut its assertion of Exemption 4, the publication of that data—together with the knowledge the manufacturers already have of their own market share—controverts the argument that the data withheld in this case would provide the competing manufacturers with any new insight into each other's market share. Disclosure cannot be found to create substantial competitive injury if the information in question is available to competitors from other sources at reasonable cost. *See Worthington Compressors, Inc. v. Costle*, 662 F.2d 45, 51-52 (D.C. Cir. 1981) ("If the information is freely or cheaply available from other sources, such as reverse engineering, it can hardly be called confidential and agency disclosure is unlikely to cause competitive harm to the submitter.").

Defendants' other claims regarding marketing capabilities are similarly insufficient. In particular, the government claims that release of the withheld data would "provide insight into the past or future strengths or weaknesses of Merck's and Glaxo's product distribution plans." Ryan Decl. ¶ 27. Defendants do not explain how disclosure of net number of doses per lot would reveal this information, nor do they explain how revelation of this information could cause competitive injury. In contrast, the evidence submitted by plaintiffs establishes that release of the requested information will have no such effect. As stated in Dr. Marks's affidavit, the net number of doses per lot has nothing to do with the manufacturer's product distribution plans.

2. Defendants have not explained how the requested records could provide new information to each manufacturer about the other's production process and capacities, nor have defendants explained how such information could cause substantial competitive injury.

Defendants also claim that release of the documents would provide each manufacturer insight into the other's production process and capacities. For example, the Ryan declaration asserts that release of the information "would likely reveal the maximum or optimum amount of volume per dose per lot of the vaccine that each manufacturer produced during the last ten to twenty years." ¶ 28. However, the declaration offers no explanation of how the requested information could reveal such information, nor does it claim that this information is presently unknown to the manufacturers or not otherwise available, or explain how this information could cause substantial competitive injury. Thus, these assertions are not sufficient to support the government's assertion of Exemption 4.

The Thomas declaration is even more conclusory. It simply asserts without explanation that "disclosure of the requested data would allow the recipients of the data to make determinations regarding [Glaxo's] manufacturing capacity for Engerix-B," and that this information "could cause significant competitive disadvantage to [Glaxo]." ¶ 5.

Finally, the Turner Declaration asserts that "knowing batch size and product yield at any stage in the vaccine production process would provide Merck's competitors with crucial knowledge regarding Merck's production capabilities and manufacturing capacity," and that knowledge of the number of doses in any given lot "might allow a competitor to deduce not only Merck's capability but also its process parameters," including "the incubation times used by Merck during the manufacturing process." ¶ 5. These allegations are insufficient to justify the government's Exemption 4 claim, because it is not apparent how the requested information (net number of doses per lot) could reveal "batch size," "product yield," "production capabilities and manufacturing capacity," or "incubation times." Release of final data does not cause substantial competitive harm when it is "made up of too many fluctuating variables for competitors to gain any advantage from the disclosure." *GC Micro Corp. v. Def. Logistics Agency*, 33 F.3d 1109, 1115 (9th Cir. 1994); *see also Ctr. for Pub. Integrity v. Dep't of Energy*, 191 F. Supp. 2d 187, 194-95 (D.D.C. 2002) (rejecting argument that "if the total amount of a bidder's offer is known, then the bidder's competitors can reconstruct each factor in the bidder's calculations in order to

discern its valuation methodology" because "this is tantamount to attempting to solve for x in the equation x + y + z = $3.65 billion without knowing the other variables"). Moreover, the declaration does not explain how the revelation of such information would cause substantial competitive injury. *See GC Micro Corp.*, 33 F.3d at 1114-15 (9th Cir. 1994) (finding that agency did not meet its burden of showing substantial competitive harm where agency failed to show how analysis of the withheld data would give competitors an advantage). Nor does it establish that the production information it claims would be revealed by disclosing the number of doses per lots is unknown to Merck's sole competitor. *See Worthington Compressors*, 662 F.2d at 51-52.

Indeed, as shown by the affidavit of Dr. Marks, the assertion that knowledge of lot size reveals information about production capacity is tenuous at best. ¶19. Lots vary in size and there is no reason to believe that the size of any one lot represents a manufacturer's maximum capacity. ¶20. Similarly, knowledge of how many doses a manufacturer has decided to make does not give insight into the processes the manufacturer uses to make those doses. ¶17.

Further, as explained in the Marks affidavit, such information is already known to both companies. ¶18. Dr. Marks explains that the hepatitis B vaccine industry in the United States is comprised of a relatively small group of people and, as a result, there is very little that one manufacturer does not know about the production processes and capabilities of the other. *Id.* Dr. Marks cites as an example that the incubation times used by Merck and Glaxo in manufacturing the hepatitis B vaccine are known to one another. ¶18.

III. If the Court Finds that Defendants' Assertions, If True, Could Provide a Factual Basis Adequate to Support the Exemption 4 Claim, Plaintiffs Should Be Granted Leave to Conduct Discovery and Time to Gather Evidence to Challenge Defendants' Assertions and Develop Contrary Evidence.

Because defendants' declarations are conclusory and insufficient to meet defendants' burden of proving that the manufacturers will face substantial competitive harm if the requested data is released, summary judgment should be granted in favor of plaintiffs. However, if this court decides that the factual assertions in defendants' declarations, if true, could be adequate to support their Exemption 4 claim, then plaintiffs should be granted a stay pursuant to Fed. R. Civ. P. 56(f) and leave to conduct discovery and gather additional evidence.

Although FOIA cases are often resolved through summary judgment, *see Miscavige v. I.R.S.*, 2 F.3d 366, 369 (11th Cir. 1993), "FOIA cases are not immune to summary judgment requirements." *Alyeska Pipeline Serv. Co. v. U.S. E.P.A.*, 856 F.2d 309, 313 (D.C. Cir. 1988). Thus, "if material facts are genuinely in issue or, though undisputed, are susceptible to divergent inferences bearing upon an issue critical to disposition of the case, summary judgment is not available." *Id.* at 314.

"Before entering summary judgment, the district court must ensure that the parties have an adequate opportunity for discovery." *Florida Power & Light Co. v. Allis Chalmers Corp.*, 893 F.2d 1313, 1316 (11th Cir. 1990) (citing *Celotex Corp. v. Catrett*, 477 U.S. 317, 322 (1986)). "Federal Rule of Civil Procedure 56(f) allows courts to defer ruling on summary judgment motions until the non-moving party has been able to conduct all necessary discovery." *Leigh v. Warner Bros., Inc.*, 212 F.3d 1210, 1219 (11th Cir. 2000). Here, plaintiffs have not yet had the opportunity to conduct discovery or to gather evidence to counter defendants' claims. Until the government filed its motion for summary judgment on June 10, 2005, plaintiffs did not know the factual allegations upon which defendants base their argument that the requested data is confidential commercial information. Indeed, due to the conclusory nature of the assertions in the declarations submitted by defendants, plaintiffs are still unclear on exactly how defendants are claiming the disclosure of the requested data would cause Merck and Glaxo substantial competitive harm. Plaintiffs therefore need discovery from the FDA and the two manufacturers to understand the basis for defendants' allegations so they can appropriately respond to those allegations. Once plaintiffs have explored the basis for those allegations, they will need time to

gather their own declarations or affidavits, if any, to challenge the facts revealed. As discussed in the Maglio affidavit, plaintiffs believe, based on their knowledge of the structure of the hepatitis B vaccine market and the efforts they have already begun to undertake to review the literature and contact experts in the field, that they will discover that (i) the market is not competitive, (ii) Merck and Glaxo already know each other's respective market share and sales volume information, (iii) hepatitis B vaccine marketing is undertaken in such a way that knowledge of lot size would not affect marketing strategies, (iv) knowledge of lot size does not give insight into hepatitis B vaccine manufacturing capacities, and (v) Merck and Glaxo already use similar, if not identical, manufacturing processes. The affidavit of Altom M. Maglio is attached hereto as Exhibit "D." In short, plaintiffs believe they will uncover evidence to demonstrate, contrary to defendants' assertions, that disclosure of the withheld data will not cause the manufacturers substantial competitive harm.

Therefore, pursuant to Fed. R. Civ. P. 56(f), plaintiffs respectfully request an extension of time to respond more completely to the factual allegations on which defendants base their motions for summary judgment and leave to take necessary discovery, if the court decides that the factual assertions in defendants' declarations, if true, could be adequate to support their Exemption 4 claim.

CONCLUSION

For the foregoing reasons, the Court should deny defendants' motions for summary judgment, grant plaintiffs' motion for summary judgment, and order the FDA to produce the requested records. In the alternative, the Court should grant plaintiffs leave to take discovery and an extension of time to respond more completely to the factual allegations on which defendants base their motions for summary judgment.

Dated: July 8, 2005

Respectfully submitted,

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CERTIFICATE OF SERVICE - CM/ECF

I hereby certify that on July 8th, 2005, I electronically filed the foregoing with the Clerk of the Court by using the CM/ECF system which will send a notice of electronic filing to the following:

Charles T. Harden, III, Esq.
Erik R. Matheney, Esq.
Brett J. Preston, Esq.
Maria E. Rodriguez, Esq.

I further certify that I mailed the foregoing document and the notice of electronic filing by first-class mail to the following non-CM/ECF participants: N/A.

/s/ Altom M. Maglio
Altom M. Maglio

Common Questions about

Adverse Events That Follow Vaccination

What is the Vaccine Adverse Events Reporting System (VAERS)?

The Vaccine Adverse Events Reporting System (VAERS) is one of several vaccine monitoring programs that are used to monitor vaccine safety in the United States. The U.S. Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC) established VAERS in 1990 to record and track reactions or adverse events that occur after a vaccine is given to patients.

Anyone can file a VAERS report if they think they or someone they know has had a reaction to a vaccine. VAERS receives reports from health care professionals, parents, and patients.

Doctors and other medical research experts from FDA and CDC analyze the VAERS reports to monitor vaccine safety. Potential safety problems that are detected during regular reviews of VAERS reports are considered to be only a "signal" of a possible safety problem. When the VAERS data "signals" a potential safety problem, the vaccine is thoroughly investigated through other research methods. This is because adverse events reports to VAERS are self-reported and not routinely verified before being entered into the system, thus great caution must be used in interpreting patterns found in the data. Verification studies have shown that most adverse events reported in the VAERS database are not actually caused by an immunization. Rather, the "adverse events" that are shown to be unrelated to an immunization were the result of some other cause, such as a naturally occurring illness.

The rotavirus vaccine is a recent example of how VAERS works. Analysis of VAERS data in 1999 identified that 15 cases of a rare but serious bowel obstruction were reported in association with the rotavirus vaccine (after approximately 1.5 million doses of the newly licensed vaccine had been given to patients). Medical experts are now conducting further studies to better understand the relationship between the bowel obstructions and the vaccine. In the meanwhile, the vaccine has been withdrawn from use in the United States.

The VAERS telephone number is 1-800-822-7967; the Web site is www.fda.gov/cber/vaers; and the email address is vaers@cber.fda.gov.

Are there "hot lots" of vaccines that have been associated with more adverse events than others have? Should parents find the numbers of these lots and make sure their children don't receive vaccines from them?

The answer to both of these questions is no. Manufacturers produce and distribute vaccines in quantities known as "lots." Lot sizes vary widely between different types of vaccines and different manufacturers. Samples of each lot are sent to the FDA for tests of safety, potency, and purity before the lot may be given to patients.

Exhibit "A"

Common Questions about

Adverse Events That Follow Vaccination (continued)

VAERS data can be used to monitor how many adverse events have been reported for each vaccine "lot" approved for use. However, because vaccine lots are not all of the same size, nor distributed and used at the same rate, differences in the numbers of adverse events reported must be interpreted with great caution. Some people have misinterpreted the difference between the number of adverse events in some lots versus other lots as meaning that some lots, i.e. "hot lots," are more dangerous than others.

FDA officials routinely monitor vaccine lots using VAERS data and other information. With the exception of an early lot of polio vaccine in 1955, which was not fully inactivated, there has never been a "hot lot."

Members of the public can also view the adverse reaction data in the VAERS database online at www.vaers.org. Currently, however, it is difficult for members of the public to interpret this information because the number of doses created in a given vaccine lot and the actual use, or market share, is considered to be the proprietary information of the manufacturer, and as a result, is not made available to the public. FDA officials do have access to this information, and they use it in their vaccine safety monitoring, but they are not allowed to make proprietary information public.

The perspective of the National Network for Immunization Information is that vaccine manufacturers should release to the public information on the number of doses created and used. Releasing this information to the public, or allowing the FDA to do so, will have an important benefit and is unlikely to put any vaccine manufacturer at a competitive disadvantage in the marketplace. The benefit of releasing the data is that interested members of the public will be able to prove to themselves that there are no "hot lots."

Are some people more susceptible to adverse reactions than others?

Yes, but it is important to understand that serious adverse reactions to vaccines are very rare. Some people are allergic to a substance present in a vaccine, such as an antibiotic or gelatin stabilizer. These people may experience a severe allergic reaction to the vaccine (that can cause difficulty in breathing, a drop in blood pressure, and sometimes shock); this occurs very rarely approximately (1 out of 500,000 doses).[1] The American Academy of Pediatrics, the Centers for Disease Control and Prevention, and the American Academy of Family Physicians recommend that doctors avoid immunizing a person who has had an anaphylactic reaction to a component of a vaccine. However, people who have had less serious reactions to a vaccine might choose to be vaccinated to avoid the risk of illness or death from vaccine-preventable diseases.

Also, children with a personal or family history of seizures may be at greater risk of having seizures after being vaccinated with the DTP (diphtheria, tetanus, pertussis) vaccine.[2] However, this vaccine is no longer recommended for use in the United States. The newer DTaP vaccine (which includes the greatly purified acellular pertussis vaccine [aP] as a component) which is now used is far less likely to cause seizures in any children. DTaP is safe and recommended even for children with a family history (siblings or parents) of seizures.

Exhibit "A"

Common Questions about

Adverse Events That Follow Vaccination (continued)

If one person in a family has an adverse reaction to a vaccine, will other members of the family also have the same reaction? Is there a laboratory test that can identify whether a person might have an adverse reaction to a vaccine before being vaccinated?

There is no single test that can determine whether a person will have an undesired reaction to a vaccine. However, if a person has a serious allergic reaction after a vaccination, he or she may be referred to an allergist who can attempt to determine which component of the vaccine may have caused the reaction. If an allergy to a vaccine component is found in one person, siblings, and children of that person can also be tested for the allergy. However, most reactions are not likely to occur in two members of the same family.

Can vaccines cause permanent adverse events, such as a long-lasting impairment, or death?

Yes, however it is important to understand that the risk of serious adverse events is extremely small (approximately 1 serious event occurs for each 100,000 doses of vaccine given). Most adverse events associated with vaccines are minor and short-lived. Of those few serious adverse events which do occur, only a small proportion result in long-lasting impairment or death. The diseases that vaccines prevent are far more dangerous than the vaccines that effectively prevent them.

Some people believe that certain immunizations can lead to a number of chronic diseases. Many scientific studies have been conducted to investigate these concerns. The results of this research repeatedly point to the conclusion that vaccines do not cause chronic diseases. For example, the Institute of Medicine, an independent research organization that is part of the National Academy of Sciences, reviewed all existing evidence on health problems that occur after vaccination. Their review did not show a cause-and-effect relationship between vaccines and any long-term illness.[4,5]

- Some scientists, and some parents, are concerned about a possible link between MMR (measles, mumps, and rubella) vaccine and autism. It is not yet known for certain what causes autism, but the best available evidence indicates that autism is a condition that begins before birth (in the first trimester of pregnancy), not after a child is born. The disease is usually diagnosed when children are 18 to 30 months old, which is the period shortly after they receive many of the recommended vaccines. Because of this coincidence in timing, some people have come to believe that the development of autism is somehow associated with the MMR vaccine. With the exception of one research study, whose findings have now been widely refuted, all of the scientific evidence has concluded that vaccines are in no way associated with autism.[6-11]
- Similarly, one investigator has suggested that the onset of diabetes might somehow be linked to whole-cell pertussis vaccine, to *Haemophilus influenzae* type b (Hib) vaccine, the new pneumococcal conjugate vaccine, or to the timing of immunizations in general[12] (also see www.vaccines.net). Scientific research studies and research reviews, however, have all concluded that vaccines do not cause diabetes.[13-17]
- Other people have been concerned that vaccines may be associated with Sudden Infant Death Syndrome (SIDS), which typically occurs in infants between 2 and 4 months of age (a period when many immunizations are given). All scientific studies and review papers have shown that vaccines do not cause SIDS.[18-21] Since 1992, the rate of SIDS in the United States has been reduced by 40% as a result of an education campaign encouraging parents to put their babies to sleep on their backs.

Exhibit "A"

Common Questions about

Adverse Events That Follow Vaccination (continued)

- Rates of childhood asthma have increased in recent years. This increase occurred during a period of time when the number of routine childhood immunizations also increased, so some have speculated that these may be related. As a result, medical researchers have studied whether vaccines might cause asthma. These studies found no increased risk of asthma after vaccination.[22-23]
- There has also been concern that multiple sclerosis (MS) might be associated with use of the hepatitis B vaccine.[24-25] In 1994, the Institute of Medicine, an independent research organization that is part of the National Academy of Sciences, reviewed all available information and determined the evidence did not show that the vaccine causes nervous system diseases. More recently, in 1998, the Viral Hepatitis Prevention Board of the World Health Organization asked a panel of experts to review scientific data again. These experts also concluded that the hepatitis B vaccine does not cause multiple sclerosis.

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Exhibit "A"

Common Questions about

Adverse Events That Follow Vaccination (continued)

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16 Karvonen M, Cepaitis Z, Tuomilehto J. Association between type 1 diabetes and Haemophilus influenzae type b vaccination: birth cohort study. BMJ 1999;318:1169-1172.

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19 Cherry JD, Brunell PA, Golden GS, Karzon DT. Report of the Task Force on Pertussis and Pertussis Immunization —1988. Pediatrics 1988;81(suppl):939-84.

20 Hoffman HS, Hunter JC, Damus K, et al. Diphtheria-tetanus-pertussis immunization and sudden infant death: results of the National Institute of Child Health and Human Development Cooperative Epidemiological Study of Sudden Infant Death Syndrome Risk Factors. Pediatrics 1987;79:598-611.

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22 Henderson J, North K, Griffiths M, Harvey I, Golding J. Pertussis vaccination and wheezing illnesses in young children: prospective cohort study. The Longitudinal Study of Pregnancy and Childhood Team. BMJ 1999;318:1173-6.

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24 Meeting Report. Multiple sclerosis and hepatitis B vaccine. Vaccine 1999;17:2473-2475.

25 Halsey et. al. Hepatitis B vaccine and central nervous system demyelinating diseases. Pediatr Infect Dis J 1999;18:23-4.

Recommended books and Web sites on this topic:

Offit PA and Bell LM. Vaccines: What every parent should know, revised edition. New York: IDG Books; 1999.

Humiston SG and Good C. Vaccinating your child: Questions & answers for the concerned parent. Atlanta: Peachtree Publishers; 2000.

The Centers for Disease Control and Prevention (www.cdc.gov/nip/vacsafe/vaccinesafety/sideeffects/autism.htm)

National Alliance for Autism Research (NAAR) Web site (http://babydoc.home.pipeline.com/naar/naar.htm)

National Multiple Sclerosis Society Web site (www.nmss.org)

Exhibit "A"

1. I have been actively involved in the research, production, and regulation of vaccines, including recombinant vaccines similar to the current hepatitis B vaccines presently utilized in the United States.

2. I received a doctorate in Microbiology from UCLA in 1977 and a Doctor of Medicine degree from the UCLA School of Medicine in 1980.

3. I am Board Certified in Internal Medicine by the American Board of Internal Medicine. I am licensed to practice medicine in 3 states, am staff at two hospitals, and have an active hospital-based practice which currently centers on Hepatitis virus infections.

4. I also provide consulting on clinical research and regulatory affairs and medical-legal consulting on pharmaceutical and vaccine industry issues.

5. From 1997 until 2000, I was Senior Vice President for Clinical Research and Regulatory Affairs at Emerging Technology Partners ETP, the biotech division of the Economic

reports, and assisting in obtaining regulatory approval for the vaccines from the Food and Drug Administration. During my time at Connaught, I was involved with the research, development, and production of the recombinant Lyme vaccine, the Bacillus Calmette-Guerin (BCG) vaccine, the POX-Japanese Encephalitis viral vector Vaccine, the POX-Malaria viral vector Vaccine, and collaborated with development of the Vaccinia Melanoma Oncolysate vaccine, HIV vaccines, and cancer vaccines. The production of several of these vaccines is very similar to that utilized in regard to the hepatitis B vaccine as they are also recombinant or genetically engineered vaccines.

8. Prior to working at Connaught, I was Associate Director of Antibacterials at Hoffman-La Roche and before that had a private Internal Medicine practice.

9. I have written numerous articles and research reports relating to the research, development, and production of vaccines and recombinant vaccines.

Exhibit "B"

give the two manufacturers of hepatitis B vaccine in the United States any new information about each other's market share. The manufacturers already know the aggregate number of doses sold in the United States, and they already know how many doses they sold. Because there are only two manufacturers of the hepatitis B vaccine, Merck and Glaxo, each manufacturer can determine the number of doses sold by the other manufacturer, and thereby its market share, by subtracting the number of doses each sold from the aggregate number of doses of the vaccine sold in the United States.

15. Disclosure of the net number of doses per lot would not cause a vaccine manufacturer competitive harm in providing the other manufacturer with insight into its marketing strategy. First, such information would not tell the other manufacturer anything about the other's marketing strategy as the net number of doses per lot and marketing of the vaccine are unrelated. Second, even if it did disclose some marketing information, that information is already known to

older vaccines such as the recombinant hepatitis B vaccine, is comprised of a relatively small group of people. Due to lateral hires from other manufacturers, the exchange of information at scientific and industry meetings and in scientific and industry publications, patent filings, and licensing agreements, there is very little that each manufacturer of the hepatitis B vaccine in the United States does not know about the production processes and capabilities of the other. For example, the incubation times used by Merck and Glaxo in manufacturing the hepatitis B vaccine are generally known in the vaccine industry.

19. It was claimed in the declarations that disclosure of the net number of doses per lot would reveal "the maximum or optimum amount of volume per dose per lot of the vaccine that each manufacturer produced during the last ten to twenty years." If I correctly understand what was trying to be said, I see no way that the net number of doses per lot would reveal this information. There are simply too many variables to determine this from the net number of doses

Donald H. Marks

Donald H. Marks, M.D., Ph.D.

SWORN TO and subscribed before me this second day of July, 2005 by Donald H. Marks, M.D., Ph.D., who is personally known to me or who produced D/L as identification.

Notary Public

My Commission Expires 9-17-05

Exhibit "B"

CURRICULUM VITAE

NAME: DONALD HARVEY MARKS, M.D., Ph.D., FACP
ADDRESS: 210 Lorna Square, PMB 192, Hoover, AL 35216
BIRTHDATE: 27 June 1949
BIRTHPLACE: Buffalo, New York
CITIZENSHIP: United States of America

Office: 1-205-682-7389 **FAX**: 1-603-372-4813 **e-mail**: DHMarks@Yahoo.com

PHARMACEUTICAL INDUSTRY EXPERIENCE

EXTANT Consulting, Principle, 1997 to present,
Medical-legal consulting on pharmaceutical industry issues
Clinical Research - clinical trial design and monitoring, adverse event monitoring, clinical summary preparation, Safety reports
Regulatory Affairs: Device, Drug and biological filings, annual reports, etc.

Emerging Technology Partners, Nov 1997 to Jan 2000, the biotech division of Economic Development Partnership of Alabama, Senior Vice President, Clinical Research and Regulatory Affairs.
Working with the scientists to define their intellectual property,
Develop research and development strategies to transfer their technology from the lab into animal studies and then to clinical,
Orienting the scientists into a business environment,
Working with the tech transfer office on property transfer agreements,
Preparing business plans (currently three),
Presentations and negotions with interested biotechs, investors, and with the FDA,
Identifying new technology to transfer in and develop.

Immunomedics, Inc., Moris Plains, NJ 7-96 to 1-97; Vice President, Clinical Research
Director, Departments of Medical Research and Clinical Data Management Programs:
Radioimmunoscintigraphy and Radioimmunotherapy of cancer using radiolabeled monoclonal antibody
Overall management Phase I-III clinical trials
Adverse event management, preparation of annual safety reports, wrote Integrated Summary of Safety for BLA
Managed department staff of up to 20 people (Oncologist, PhD manager, 2 contract physicians (ID, Nuc Med), 2 Nuclear Medicine Imaging specialists, 6 CRAs (one a foreign MD), Data Manager, 2 SAS programmers, 2 data entry clerks, 3 secretaries
Coordinated with outside contractors, CROs, consultants, industry and academic experts
Responsibility for department budget
Successfuly submitted a BLA 12-97 for radioimmunoscintigraphy of infectious diseases

PerImmune, Inc., Rockville, MD 7-95 to 7-96
Director, Departments of Medical Research, Regulatory Affairs and Clinical Data Management

Clinical Programs:
Radioimmunoscintography and Radioimmunotherapy of cancer using totally human monoclonal antibody,
Adverse event management, preparation of annual safety reports, wrote Integrated Summary of Safety for BLA
Overall management Phase I-III clinical trials
Applied Specific Immunotherapy, vaccines and ex vivo cell expansion,
Non-Specific immune therapy of cancer: bladder,
In vitro diagnostic devices
Hyperimmune globulin for treatment of cancer and infectious diseases.
Managed department staff of up to 20 people (PhD manager, 1 contract physician, 1 Nuclear Medicine Imaging specialist/ manager, 5 CRAs, Data Manager, 2 SAS programmers, 1 data entry clerk, 3 secretaries, 3 Regulatory Affairs specialists
Coordinated with outside contractors, CROs, consultants, industry and academic experts
Responsibility for department budget

Connaught Pasteur Merieux (now Aventis Pasteur), Director, Clinical Research, Swiftwater, PA, 3-91 to 7-95
Responsibilities:
Coordinated all Immunology Programs, and certain vaccines under development; Overall management Phase I-III clinical trials
Adverse event management, preparation of annual safety reports, interacted with Regulatory Dept. and FDA on adverse event program for new recombinant protein vaccine, established independent Adverse Event Advisory Board, including writing the SOP and manual for Anti-Receptor antibody for Immune Response Modulation and Rabbit antihuman Thymocyte Ig for grafts (Project Team Leader), aplastic anemia
North American Development of all Recombinant Pox Vaccines
Hyperimmune Ig for CMV
BCG for Bladder cancer and TB vaccine
Vaccinia Melanoma oncolysate vaccine
Assisted in preparation of budget for entire Medical Department
Wrote Final Study Reports, FDA submissions, and answered FDA inquiries
Provided medical advice to customers on marketed products and to collect and process adverse effect reports.
Prepared Medical Dept. Policies and Procedures Manual
Transfer of Professional Medical Education Programs from Marketing Dept. to Medical Dept., and Direction of CME Program
Evaluation of Potential Licensing of Technology: Hemoglobin, Colostral Ig, Factor 9, immune toxins, others, including preparation of Return-on-Investment and Statement of Interest reports.
Member: the following PMsv-Connaught Committees
Corporate Development Committee for Immune Proteins
BCG Working Group
POX-Japanese Encephalitis Vaccine Project Team
POX-Malaria Vaccine Project Team
Lyme Vaccine project Team
Corporate Cancer Vaccine Working Group
Corporate HIV Vaccine Working Group
Strategic Planning Committee on FDA Reform

Hoffmann-La Roche, Associate Director Antibacterials 1-89 to 3-91
Responsibilities:

1. a) Fleroxacin NDA: Safety Officer, prepared individual AE reports for Regulatory Dept, and assisted in preparation of annual safety report.

b) Ceftriaxone:

Assisted in three Supplementary Submissions, including presentations to FDA:

Expanded Anaerobe Coverage (approved 6-90), Biliary Surgery Prophylaxis, Pediatric Meningitis QD; also in Acute and Subacute Endocarditis

2) Director, Lyme Disease treatment program, developed protocols for Indications, FDA presentations

3) Protocol Industry Advisor to ACTG 145 "Ceftriaxone for Neurosyphilis in AIDS Patients"

4) 5-FluCytosine IV: Physician in Charge, Evaluated AE's, IRAE's, prepare annual safety reports for FDA.

Roche-wide Quality Award 4-90
Member: Good-Government Committee, Political Action Committee
Chairperson, PAF Antagonists in the Treatment of Septic Shock, Working Group to Explore opportunities

Private Practice, Internal Medicine 7-87 to 12-88
Group practices:

Dotoli Medical Group, Nutley, NJ 1989-1991, some clinic, mostly inpatient.
Dover Community Clinic, NJ, 1992-1999, free-standing, all age walk-in.

Letterman Army Institute of Research, Division of Blood Research, 6-83 to 6-87

USAF Medical Center Keesler, Clinical Research Laboratory, 6-80 to 6-83

FDA Experiences:

Annual reports, and protocol presentations to CBER, CDER, NIH and NCI
Outside inspections of IND's and NDA's for corporate partners
Preparation of PMAs and 510K for in-vitro diagnostic devices
Preparation of MAA and PLAs for radioimmunodiagnostic agents and ASI
Preparation of INDs.

Foreign Languages: French

UNDERGRADUATE EDUCATION
1968-1971 - Santa Monica College
1970-1972 - California State University, San Bernardino, (B.A., December, 1972)

GRADUATE EDUCATION
1972-1973 - University of California, Riverside, Department of Plant Physiology
1973-1977 - University of California, Los Angeles, Department of Bacteriology, Ph.D. Microbiology, December 1977. Thesis Area: Comparative Immunology of Graft Rejection

MEDICAL EDUCATION

1976-1980 - University of California, Los Angeles, School of Medicine, (M.D., June 1980)
June 1980-June 1983 - Residency in Internal Medicine, USAF Medical Center, Keesler AFB, MS

MILITARY EDUCATION
Officers Candidate School, June 1976
Medical Indoctrination for Medical Service Officers, June 1980
Air Command and Staff College, graduate, June 1984
Biological Warfare Course

LICENSURES AND CERTIFICATION
National Board of Medical Examiners #234173, July 1, 1981
Diplomat, American Board of Internal Medicine 9-13-1989
State: Alabama 23209, exp 31 Dec 03 DEA: BM5726661
New Jersey MA53574, 6-30-03
Mississippi # 9518; exp. 30Jun03
New York 180133-1; exp. 5-31-03

PROFESSIONAL ORGANIZATIONS
American College of Physicians, FELLOW
American College of Pharmaceutical Physicians,
Regulatory Affairs Professional Society
Drug Information Association

PUBLICATIONS

1. Marks DH: Aeromonas hydrophila in the coelomic cavity of the earthworms Lumbricus terrestris and Eisenia foetida. J.Invert.Path. 29:382-383, 1977.

2. Toupin J, Marks DH, Cooper EL, Lamoureux G: Earthworm coelomocytes in vitro. In Vitro. 13(4):218-222, 1977.

3. Linthicum DS, Marks DH, Stein EA, Cooper EL: Graft rejection in earthworms: An electron microscopic study. Europ. J. Immunol. 7(12):871-876, 1977.

4. Linthicum DS, Stein EA, Marks DH, Cooper EL: Electron microscopic observations of normal coelomocytes from the earthworm, Lumbricus terrestris. Cell and Tissue Research 185:315-330, 1977.

5. Marks DH, Stein EA, Cooper EL: Chemotactic attraction of Lumbricus terrestris coelomocytes to foreign tissue. Developmental and Comparative Immunology 3:277-285, 1979.

6. Marks DH, Stein EA, Cooper EL: Acid phosphatase changes associated with response to foreign tissue in the earthworm Lumbricus terrestris. Comp. Dev. and Physiol. 64A:681-683, 1981.

7. Stein EA, Marks DH, Cooper EL: Lack of acid phosphatase release during in vitro phagocytosis by coelomocytes of the earthworm, Lumbricus terrestris. J. Invert. Path. 9:116-118, 1982.

8. TenEyck R, Schaerdel AD, Lynett JE, Marks DH, et al: Stroma-free methemoglobin solution as an antidote for cyanide poisoning. A preliminary study. Clinical Toxicology 21(3):343-358, 1984.

9. Marks DH, et al: Pelvic hematoma after intercourse while on chronic anticoagulation. Annals of Emergency Medicine 13:554-556, 1984.

10. Marks DH, Patressi J, Chaudry IH: Effect of pyridoxalated stabilized stroma-free hemoglobin solution on the clearance of intravascular lipid by the reticuloendothelial system. Circulatory Shock 16:165-172, 1985.

11. Marks DH, et al: Pyridoxalated polymerized stroma-free hemoglobin solution for hemorrhagic shock in dogs. Military Med. 152(5):265-271, 1987.

12. Marks DH, et al: Antibody Response to Transfusion With Pyridoxalated glutaraldehyde-treated Hemoglobin Solution. Mil Med 152(9):473-477, 1987.

13. Marks DH, Hou KC: Removal of bacteria from blood. Military Med. 152:156-160, 1987.

14. Marks DH, et al.: Optimization of synthesis of pyridoxalated polymerized stroma-free hemoglobin solution. Mil Med 153:44-49, 1988.

15. Marks DH et al: Efficiency of Antibacterial Membrane and effect on Blood Components. Mil Med 153(7):337-340, 1988.

16. Davidson IJA, Drukkerr S, Hedlund B, Marks DH et al: Deleterious Effects of Stroma-free Hemoglobin Used As Resuscitative Fluid For Rats With Ischemic Intestinal Shock. Crit Care Med 16(6):606-609, 1988.

17. Marks DH et al: Removal of Bacteria From Blood By Charcoal Hemoperfusion. J. Biomaterials, Artificial Cells and Artificial Organs. 16(1-3):135-140, 1988.

18. Moore GL, Marks DH, et al: Ascorbate-2-phosphate in Red Cell Preservation: Clinical Trials and Active Components. Transfusion 26(3):221-225, 1988.

19. Marks DH, et al.:Effect of Polymyxin B on in vivo hepatoxicity of hemoglobin. Mil Med 154(4):180-184, 1989.

20. Keller, D, Koster, FT, Marks, DH et al.:Safety and Immunogenicity of a Recombinant Outer Surface Protein A Lyme Vaccine. JAMA, June 8, 94, p 1764-1768.

21. Sigal LH, Zahradnik JM, Lavin P, Patella SJ, Bryant G, Haselby R, Hilton E, Kunkel M, Adler-Klein D, Doherty T, Evans J, Molloy PJ, Seidner AL, Sabetta JR, Simon HJ, Klempner MS, Mays J, Marks D, Malawista SE A vaccine consisting of recombinant Borrelia burgdorferi outer surface protein A to prevent Lyme disease. Recombinant Outer-Surface Protein A Lyme Disease Vaccine Study Consortium. N Engl J Med (1998 Jul 23) 339(4):216-22

22. Kanesa-thasan N, Smucny JJ, Hoke CH, Marks DH, Konishi E, Kurane I, Tang DB Vaughn DW, Mason PW, Shope RE. Safety and immunogenicity of NYVAC-JEV and ALVAC-JEV

attenuated recombinant Japanese encephalitis virus--poxvirus vaccines in vaccinia-nonimmune and vaccinia-immune humans. Vaccine (2000 Oct 15) 19(4-5):483-91

ABSTRACTS AND RESEARCH REPORTS

1. Marks DH: Biochemical changes accompanying graft rejection and wound healing in the earthworm Lumbricus terrestris. Federation Proc.35:277 (Abstract), 1976.

2. Marks DH: Effect of graft rejection and wound healing on coelomocyte enzymatic activity in the earthworm Lumbricus terrestris. American Zoologist 16(2):251, 1976 (Abstract).

3. Marks DH, Stein EA, Cooper EL, Ramirez JA: Accelerated graft rejection in earthworm: Immunologic Memory? Research Report, Dept. of Anatomy, School of Medicine, University of California, Los Angeles, 1977.

4. Marks DH: Stroma-free hemoglobin solution as a blood substitute, Society Air Force Physicians, Sacramento, California (Abstract), 1982.

1. Marks DH: Stroma-free hemoglobin solution as a blood substitute. Society of Air Force Physicians, San Antonio, Texas (Abstract), 1983.

6. Marks DH: Pyridoxalated polymerized stroma-free hemoglobin solution for hemorrhagic shock. Advances in Blood Substitute Research. Ed. RB Bolin et al. Alan R. Liss, Inc., New York, pp. 433, 1983.

7. Marks DH: Stroma-free hemoglobin solution as a blood substitute. Society of Air Force Physicians, Colorado Springs, Colorado (Abstract), 1984.

8. Ottinger, W., Marks DH, et al: Large scale production of pyridoxalated polymerized stroma-free hemoglobin solution. USAF Medical Center Keesler, Clinical Research Lab Institute Report, 1986.

9. Marks DH, Medina F: Removal of bacteria from blood: Efficacy. Abstract for presentation at Am Society of Hematology meeting 12-86; Published in Blood 68(5, Supp.1):300a, 1986.

10. Moore GL, Ledford ME, Marks DH: Clinical trials of an optimized additive solution for red cell storage which also preserves 2,3-DPG. Transfusion, Dec 1986.

11. Marks DH, Medina F: Removal of bacteria from blood: Efficacy. Abstract for presentation at Society for Air Force Physicians Meeting 3-87.

12. Marks DH, Medina F: Effect of Polymyxin B on in vivo hepatoxicity of hemoglobin. Abstract for presentation at International Symposium for Blood Substitutes, Montreal 5-87.

13. Marks DH et al. Clinical Studies in Humans of Outer Surface Protein A Vaccine for Lyme Disease. Abstract of presentation at VI International Conference on Lyme Borreliosis, Bologna, Italy, June 19, 1994.

14. Kanesa-Thasan N, Smucny JJ, Marks DH, Hoke CH Jr. Phase 1 Trial of NYVAC and ALVAC Recombinant Poxvirus - Japanese Encephalitis Virus vaccines. Presented at the Am Soc Tropical Medicine and Hygiene, Cincinnati, Nov 94.

15. Marks DH, Hosbach P, Meschievity CK. Design Issues for Clinical Trials of Vaccine for Lyme Disease, Presented at Symposium on the Therapy and Prophylaxis for Lyme Borreliosis, Portoroz, Slovenia, 13-16 May 95.

PERSPECTIVE

Why Sole-Supplier Vaccine Markets May Be Here To Stay

Vaccine markets tend to evolve toward a single dominant supplier, which has advantages as well as disadvantages.

by Patricia Danzon and Nuno Sousa Pereira

ABSTRACT: Given the structure of costs, demand, and competition, vaccine markets reach long-run equilibrium with one or very few suppliers at any point in time. Sole suppliers are less likely to exit and may have lower total social costs. Vaccine markets are dynamically competitive, with new, superior products displacing older, inferior products. Measures to address short-run supply disruptions include inventories, foreign sourcing, and improved technologies. Increasing the relative prices paid for new vaccines to levels that more closely reflect their social value compared to other new drugs and biologics is essential to achieving appropriate incentives for allocation of pharmaceutical R&D.

MARK PAULY PROVIDES a thorough review of the factors that contribute to the perceived inadequate supply of existing vaccines and the development of new ones.[1] On the demand side, he concludes: "The real limit on state and local spending on vaccines is the willingness of... taxpayers to set a high-enough priority on this type of service by being willing to pay the price of expanding it." On the supply side, he notes that "the production of existing vaccines has been characterized by major exit of firms and shortage of investment (relative to other drugs)" and concludes that "this is circumstantial evidence that returns on investment are below normal" and that there is strong evidence of inadequate spending on inputs to prevent errors and disruptions of supply. His tentative policy conclusion is that "shifting to more public provision of demand-side financing can be combined with greater reliance on markets to invent, produce, and distribute vaccines, as the [Institute of Medicine] report suggested."

Our analysis of vaccine supply elsewhere in this volume reaches some similar conclusions but with some important differences in the diagnosis of the problems and tentative policy implications.[2] We argue that given the cost and demand conditions of most vaccine markets, long-term equilibrium is likely to be one supplier or at most a few suppliers of each vaccine type at any point in time. Having a sole supplier of each vaccine type does not necessarily imply suboptimal investment or that the expected return on investment is below normal. For older products for which research and development (R&D) has presumably been fully amortized, prices must be sufficient to cover long-run marginal cost, including the costs of any plant or product upgrades required by regulation. But it is unrealistic to an-

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Exhibit "C"

DOI 10.1377/hlthaff.24.3.694

ticipate investment in new "me-too" forms of old vaccines. Rather, new entrants into older vaccine markets tend to produce superior products, and this has precipitated the exit of the older, inferior products. Thus, inactivated poliovirus (IPV) drove out active oral poliovirus (OPV), acellular pertussis drove out whole-cell pertussis, and thimerosal-free products drove out thimerosal-containing products.

The anticipation of new, superior technologies can contribute to short-run supply problems of established products, by undermining incentives for producers to invest in upgrading or expanding their existing plants. Thus, as we describe in our longer paper, the anticipation of new, superior cell-based forms of flu vaccine is one reason why existing suppliers who use the old egg-based technology are unwilling to invest in expanding their capacity, since this capacity may be rendered obsolete once the superior product is approved.

Dynamics Of Vaccine Markets

■ **Emergence of superior products.** This pattern of dynamic competition and subsequent single-product dominance of vaccine markets is not necessarily suboptimal, given the high fixed costs of regulatory approval and production, compared with the relatively small market size and concentrated demand. This concentration of demand is greatest for pediatric vaccines and is attributable not just to governmental purchase of more than half of pediatric vaccines, but also to governmental recommendations that apply equally to private as well as public purchasers. Thus, once the recommendation of the Advisory Committee on Immunization Practices (ACIP) switched from OPV to IPV, demand evaporated for OPV products, and they all exited the market. Such exits are not necessarily cause for concern, if the recommendations do in fact identify the superior product.

■ **Prices.** Of course, the entry of a superior product type need not imply a sole producer. In fact, new classes of vaccines often initially attract several suppliers. But the continued coexistence of multiple suppliers is likely only if they produce differentiated products, each of which is preferred by some group of purchasers. If the products are identical, or if one is superior for the great majority of purchasers, then competition is likely to drive prices down to marginal cost, leading ultimately to the exit of all but one producer—in the absence of tacit or explicit agreement on price and market allocation, which is unlikely to be condoned by purchasers or antitrust authorities. Thus, vaccine prices for older vaccines may be low not just because consumers and government purchasers undervalue vaccines, but also—and perhaps mainly—because competition between firms with large sunk costs and low marginal costs drives prices below purchasers' maximum willingness to pay. In economic terms, purchasers capture the consumer surplus. Anticipating such competition, potential entrants have little incentive to invest in developing similar products since they could not hope to recoup their R&D costs unless they have a sufficiently superior product to command a higher price or capture a dominant market share.

■ **Dominant supplier.** By contrast, a single-supplier equilibrium is less frequently the norm in pharmaceutical markets because those markets are generally larger relative to fixed costs; differentiated products can coexist because they often differ in safety or efficacy for major groups of consumers; demand is less concentrated; and there are no governmental recommendations that steer utilization toward the single preferred product.

If this model is correct—that vaccine markets tend to evolve toward a single dominant supplier—the good news is that this supplier is unlikely to exit, at least until replaced by a superior product, in which case the exit is less problematic. For example, there has been only one producer of measles-mumps-rubella (MMR) vaccine since 1978, two producers of IPV since 1980, and a single one after 2000.

■ **Supply interruptions.** Given high and potentially increasing fixed costs of regulatory compliance and production, total costs may be lower with a single producer. Of course, the full social cost of adding additional suppliers

Exhibit "C"

depends not only on effects on production costs but also on any reduction in the risk of supply interruptions. Nevertheless, it seems likely that any desired reduction in the risk of supply disruption could be achieved at lower cost if the sole supplier maintained excess and separate production capacity; however, imposing such a requirement or expectation on vaccine manufacturers would add to costs and hence might further reduce the number of new entrants.

Policy Considerations

■ **Inventory priorities.** If the sole-supplier equilibrium is likely to be the norm in vaccine markets, then policies to address the risk of temporary shortages are obviously critical. In the short term, there is a strong case for maintaining inventories, to the extent possible given vaccines' limited shelf life. Longer-term high priority should be given to technologies that reduce the risk of plant contamination and hence of product interruptions, and technologies that increase shelf life or shorten the lead time required to expand production, or both. The new cell-based flu vaccine technologies are expected to demonstrate the benefits of such improvements and provide some encouraging evidence that vaccine markets are providing incentives and firms are responding with improved products.

■ **Accelerated approval.** Perhaps the most promising approach to dealing with shortages is collaboration between the Food and Drug Administration (FDA) and other regulatory authorities, to facilitate accelerated approval for the U.S. market of vaccines that have met similar regulatory requirements in other jurisdictions, if serious shortages occur. As we show in our longer paper, a number of vaccines are approved in European and Canadian markets but not licensed in the United States, presumably because the expected costs of clinical trials and other requirements for U.S. approval are high compared with the expected revenues, given the relatively small market size and the competitive risks of taking on established producers in the absence of a clearly superior product. Using these foreign suppliers may be the least costly approach to handling temporary shortages. Compared with simply delaying scheduled vaccines, this strategy reduces inconvenience to patients and implies a greater financial penalty to incumbent manufacturers, thereby increasing their incentives to invest to avoid supply disruptions. But this strategy is also not without cost and risk, so the best approach is vaccine specific, depending on the expected duration of the shortage, costs, and health effects of delaying vaccine schedules and risks associated with foreign sourcing.

■ **R&D incentives.** We have argued that competition may drive vaccine prices for older vaccines below consumers' maximum willingness to pay, and hence that actual prices for these older vaccines do not provide unambiguous evidence that they are undervalued by consumers, nevertheless. However, although a detailed analysis is beyond the scope of this paper, current prices for new vaccines seem low relative to prices for some other new drugs and biologics, with some new oncology products costing $20,000–$40,000 per year of patient treatment. Thus, although considerable R&D is under way to develop new vaccines, these sorts of price differentials are likely to skew R&D investments toward the higher-price drugs and biologics, such as cancer treatments, even if vaccines offer greater potential benefits in expected life years saved. If this observation is accurate, then increasing the relative prices paid for new vaccines to levels that more closely reflect their social value compared with other new drugs and biologics is an essential step toward achieving appropriate investment in vaccines and maximizing the health benefits from pharmaceutical R&D.

NOTES

1. M.V. Pauly, "Improving Vaccine Supply and Development: Who Needs What?" *Health Affairs* 24, no. 3 (2005): 680–689.
2. P.M. Danzon, N.S. Pereira, and S.S. Tejwani, "Vaccine Supply: A Cross-National Perspective," *Health Affairs* 24, no. 3 (2005): 706–717.

Exhibit "C"

1. I am an attorney with the Maglio Law Firm, based in Sarasota, Florida.

2. I represent Dr. and Mrs. Robert Sharkey, the plaintiffs in this case. On their behalf, I sent the Freedom of Information Act (FOIA) request at issue in this case and filed the current action seeking disclosure of the requested records.

3. Until defendant Food and Drug Administration (FDA) filed its motion for summary judgment and related declarations on June 10, 2005, my clients, co-counsel, and I did not know the factual allegations upon which defendants were basing their claim that the requested data is exempt from disclosure as confidential commercial information. Therefore, we were unable to gather evidence to counter those factual allegations nor have we been permitted to conduct any discovery in this case to date.

4. The declarations submitted by defendants provide little or no detail regarding how, according to defendants, the disclosure of the net number of doses per lot of hepatitis B

Exhibit "D"

6. Based on Dr. Marks's affidavit, the articles we have read on the vaccine industry, and the descriptions of the hepatitis B vaccine market in defendants' declarations, we believe that we will be able to find facts showing, contrary to defendants' contentions, that the hepatitis B vaccine market is not competitive and that disclosure of the withheld data would not reveal either marketing or manufacturing information that would cause Merck and Glaxo substantial competitive injury. We anticipate we will discover that Merck and Glaxo already know each other's respective market share and sales volume information, that vaccine marketing is undertaken in such a way that knowledge of lot size would not affect marketing strategies, that knowledge of lot size does not give insight into manufacturing capacities, and that Merck and Glaxo already use similar, if not practically identical, manufacturing processes.

Exhibit "D"

Notary Public

My Commission Expires

Exhibit "D"