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July 24, 2002

Dockets Management Branch
Food and Drug Administration
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Docket Number 02N-0209- Request for Comments on First Amendment Issues

This letter, sent electronically and with a duplicate "hard copy," is in response to the Notice published by the Food and Drug Administration (FDA) on May 16, 2002 in 67 Federal Register 34942 which requested comments to ensure that the agency's regulations and policies "continue to comply with the governing First Amendment case law." By way of background, I will note that I have taught Food and Drug Law for 20 years, and, before teaching, I worked in the Office of Chief Counsel for FDA. I also was a member of the presidentially-appointed statutorily-created Commission on Dietary Supplements Labels.

The Supreme Court in *Thompson v. Western States Medical Center* (*Western States*)¹ recently invalidated advertising restrictions about pharmacy compounding even if the restrictions advanced the integrity of the new drug approval process when the Government's aim could be achieved by other means. The FDA Notice raised nine questions about the impact of this decision but stated that they were not intended to be exhaustive, and that the agency sought to "spur" helpful comments. This response will address a number of the questions raised by the

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Notice, although in a different order, and also suggest some key points for FDA to pursue. The Notice also raises the issues as constitutional questions, making it infeasible to consider the statutory questions or administrative law points that may exist and that can often provide a means for the agency to adapt the law to new circumstances within its delegated responsibilities. I believe it advisable to avoid constitutional issues, but since the issues have been framed as constitutional ones, a response on that basis has to be made.²

A. Justification for Pre-Market Approval of Drug Claims; Support. The Notice asks some very general questions about the basis for drug regulation, in a manner that suggests a wide scope for the agency's inquiry. The first question is whether there are arguments for regulating speech about drugs more comprehensively than dietary supplements, and what "an administrative record" must contain "to sustain such a position." The agency later asks whether there are arguments and social science evidence to support giving the Government greater latitude to regulate labels as compared with advertising. These questions could be read as putting into question the constitutional validity of the requirement for pre-market approval of drugs, as well as the need for the agency to have empirical support for mandating testing, instead of merely having disclaimers about the lack of FDA approval. The questions in the Notice, if meant to be read broadly, are so fundamental that I will start with some general comments on the importance of Congress' determinations about the need for drug regulation, and the types of support that can be sufficient for regulation.

While it is appropriate to consider the implications of the *Western States* decision, and other lower court decisions dealing with commercial speech, I do not believe they should be read as intended to undercut the constitutional validity of the pre-market approval requirements for claims for drugs, and particularly labeling claims. Indeed, the Court majority in *Western States* finds that the new drug approval process is “clearly an important governmental interests, and the Government has every reason to want as many drugs as possible to be subject to the approval process.”³

Dietary supplements are not ordinarily subject to prior review of their safety,⁴ nor is there premarket approval for their “structure or function” claims when the claim is accompanied by disclaimer about the lack of FDA approval.⁵ Congress established a less rigorous system for these products because of a congressional assessment that the supplements are “safe within a broad range of intake, and safety problems with the supplements are relatively rare.”⁶ Moreover, the claims can relate only to the “structure or function” of the body and not disease prevention and treatment.⁷ The line between disease and structure or function claims is debatable, and agency action or legislative change is needed to provide better disclosures and support for the claims, and for the safety of supplements.⁸

Whatever the case for supplements, the need for strong drug regulation is more imperative. Drugs often use potent chemicals that can cause harm, and they cannot be considered safe unless their effectiveness in treating or preventing disease outweighs these harmful effects. Furthermore, if drugs are ineffective, the delay in getting better treatment can also cause harm. These factors clearly justify Congress’ determination that pre-market approval

is needed to ensure the safety and efficacy of drugs, notwithstanding its willingness to adopt a less rigorous scheme, with disclaimers, for supplement claims.

The Notice asks if there is social science or an administrative record to support FDA drug regulation. FDA drug regulation is not simply an administrative decision and, instead, it is based on statutory requirements. Congress' reasons for enacting the requirements, in light of the experience of harm from drugs, provides all the support needed for the scheme. In 1937, a manufacturer changed the drug sulfanilamide to a liquid form by using an ingredient found in antifreeze without testing the safety of the new formulation, a change that led to over 73 deaths.⁹ Congress responded by requiring prior review of the safety of new drugs. The birth defects caused overseas by thalidomide led to the strengthening of the drugs laws and a requirement for pre-market approval of the effectiveness as well as the safety of drugs. This historical experience with the harm that can occur with insufficient review convinced Congress of the importance of having strong safeguards to protect the public. That determination and value judgment provides sufficient support for the statutory requirements, without the need for additional social science research to justify it. Moreover, the Court found that the statutory requirements for adequate and well-controlled studies reflected "the conclusion of Congress, based upon hearings, that the clinical impressions of physicians and poorly controlled experiments" were not adequate evidence of efficacy.¹⁰ While the Constitutional protections for commercial speech were not at issue, it would be strange if the Court were now to find Congress' reasons for requiring scientific testing to be of only marginal significance.

As *Western States* shows, the Court also looks to the agency explanations for the regulatory scheme in addition to the Congressional determinations in considering commercial

speech issues. The lesson from this is that the agency needs to be especially explicit and thorough in explaining the rationale for a legislative enactment, and for the agency interpretations and regulations implementing the law. In particular, it is important to explain the safety reason for the scheme, including the potential for harm from changes even in inactive ingredients, as illustrated with Elixir Sulfanilamide.

The FDA Notice asks about the administrative record needed to support its positions. It should be borne in mind that the administrative record for agency regulations need not always be based on empirical evidence. As the D.C. Circuit Court of Appeals stated, a “regulation that is self-evidently rational is not less legitimate than a regulation whose rationality must depend on elaborate statistical, expert, or other evidence.”¹¹

Some may maintain that disclaimers about the lack of studies is an alternative to doing testing for drugs. If disclaimers are to be used, that should be a Congressional decision. While disclaimers are not an adequate substitute for testing, if they are ever to be used for drugs, the burden should be on the companies who seek to use them to show that consumers-- and busy practicing physicians-- can clearly understand the disclaimers, and are not misled. Common experience indicates that users find it difficult to assess small-print complicated qualifications of a claim. When the unapproved claim is in headlines, the disclaimer qualifying it also needs to be simple and comparable to a headline in clarity. The statutory standard for approval should also provide the benchmark for judging the type of disclaimers that are needed. Thus any disclaimers relating to drugs should indicate the specific ways in which the product lacks the “adequate and well-controlled studies” needed for approval. In the case of disease claims, we are dealing not merely with economic harm. The need to protect the public from the safety risks, and potential

ineffectiveness, of powerful drugs provides the rational support for the pre-market approval requirement. If, nonetheless, Congress is found to be without the power to provide that safeguard to the American public, the promoter of the unapproved claim should have the burden to show that disclaimers are adequate to alert the user to the specific support that is lacking.

B. Direct-to-Consumer Advertisements. FDA asks if its approach to Direct-to-Consumer (DTC) advertising is “consistent with empirical research and with relevant legal authority.” While these questions are important, I do not see a reason for raising them in the context of a re-examination of the constitutional issues concerning commercial speech. Unlike the FDA policy at issue in *Western States*, FDA does not preclude all DTC ads for approved drugs. Instead its policy is geared toward preventing consumers from being misled about the approved use and the important side-effects, an aim fully consistent with the judicial decisions. Moreover, FDA does not require prior review of DTC ads, although it encourages consultation. Since the statute provides standards for prior review of drug advertisements,¹² whether such a requirement is needed is, in the first instance, a statutory question and not a constitutional one.

FDA’s Notice also asks if the DTC ads lead to over-prescription and if they encourage treatment for under-diagnosed diseases. These are important policy aims, and FDA should pursue investigating ways to achieve these policy directions. The agency also asked if the current approach creates any impediments to the ability of doctors to give optimal medical advice. In this respect FDA needs to consider measures to guard physicians from the pressure to prescribe drugs that comes from the single-drug focus of the DTC ads. I recommend that the DTC ads state prominently that consumers need to “Consult your doctor about the range of treatment choices that may be available.” The role of the physician is to advise patients about

the choice of therapies in light of available drug and non-drug treatments, the potential side-effects from these treatments, the patient's particular situation, the relative efficacy of the treatments, and cost factors, including the availability of generic drugs.

The survey cited by the dissenting judges in *Western States* indicated that family physicians reported DTC ads pressure physicians to prescribe drugs they would not ordinarily prescribe.¹³ The majority in *Western States* found this single survey insufficient to support an advertising ban since the survey was not relied upon by the Government and rested on a "questionable assumption" that physicians would prescribe unnecessary medicines and that informed consumers would make "bad decisions" from which they needed to be protected.¹⁴ FDA should consider whether the present and future surveys provide support for reducing unwarranted pressure on the physician by providing disclosures about the range of advise the patient needs from the doctor.

The typical statement in DTC ads to consult your physician about the drug, and to see if the advertised drug is "right for you," suggests that the decision is a drug-specific decision, dependent on the side-effects for the particular drug. If the ads made clearer that a relative choice needs to be made, it would be more respectful of the physician's role and might alleviate the pressure doctors feel that comes from a consumer advertisement aimed at a single drug. Moreover, in this time of concern with drug costs, there is a need to make consumers aware of the value of advice from their physician on the relative cost factors for generic and other treatments. There may be additional ways to ensure that consumer understand the wider perspective involved in the physician's advice. Further attention may also be needed to ways of ensuring that physicians have sufficient information to make the relative choice on an adequate

basis. These ways of improving DTC ads seem a more useful focus for FDA's reassessment than some general change in its existing policy.

C. Off-label Uses of Prescription Drugs. 1. Relevance of *Western States*. FDA asks about the extent of its ability to regulate speech about off-label uses and whether permitting speech by manufacturers about off-label uses would undermine the new drug approval process. Read broadly, *Western States*, can be seen as raising the issue of whether disclaimers can provide a reasonable alternative to restrictions on speech by the manufacturer about off-label uses of drugs. This issue is most relevant with respect to the distribution by pharmaceutical companies to doctors of medical articles about off-label uses of approved drugs. Promotion of off-label uses by manufacturers that is not based on peer-reviewed medical articles should clearly be considered impermissible--no matter what disclaimers are used-- since allowing that promotion would undercut the drug approval process, and the promotions are not related to any distinct substantial interest. These comments will focus on distributions of medical journals, for ease of analysis, but they might provide a framework for evaluating the constitutional protections available to manufacturers who suggest that continuing medical conferences, paid for by the manufacturer, cover off-label uses.

In the case of medical journals, FDA recognizes that doctors, as part of the practice of medicine, will discover off-label uses for approved drugs, and that medical researchers investigate these uses and communicate their conclusions to practitioners in accordance with the standards of the profession. FDA's position on the extent to which manufacturers can initiate distribution of medical articles has already been the subject of litigation, which ended on appeal

without reaching the constitutional merits, with FDA having withdrawn its prior guidance, and with the FDA policy left in some uncertainty.¹⁵

In *Western States*, the Court assumed that a statutory preclusion of advertisement to physicians and consumers of the willingness of a pharmacy to “compound” specific drugs, without FDA approval of the variation, would promote the valid Governmental interest in the integrity of the NDA process.¹⁶ Nonetheless the Court found that before suppressing speech, Congress had to consider other alternatives, and that the potential for misleading advertising about the risks of a drug could be dealt with by a “warning that the drug had not undergone FDA testing and that its risks were unknown.”¹⁷ The Court, in pointed language found that “if the First Amendment means anything, it means that regulating speech must be a last--not first--resort.”¹⁸

FDA’s position about medical articles describing off-label uses has some parallels to its position with respect to pharmacy compounding.¹⁹ A mere disclaimer about the lack of FDA approval did not eliminate the need for approval of a new drug application when a manufacturer promoted off-label uses.²⁰ In 1997, Congress also enacted in the Food and Drug Modernization Act (FDAMA) an optional modified review system that can be used by manufacturers who distribute reprints, but one that did not simply rely on disclaimers.²¹ While there are some similarities, it is also necessary to consider the differences between the two situations, and the difficulties in providing developing adequate warnings when manufacturers distribute articles about off-label uses of drugs.

2. Differences in Need for Review of Significant New Uses. *Western States* dealt with “pharmacy compounding,” which primarily relates to making changes in the formulation of an

approved drug, using approved ingredients, to deal with individual patient needs in light of individual variability.²² Compounding should respond to individualized needs and this focus should limit the extent to which compounding is occurs, and the potential for widespread harm to the public. With off-label uses, promoted by major pharmaceutical companies, wider use can occur on a national basis, with a greater risk that the drugs can pose safety risks and delay effective treatment for wide numbers of people. Moreover, the large market for off-label uses, and the involvement of the pharmaceutical company, makes possible the type of costly testing needed for drug approval, that is not economically viable for the small-scale efforts involved in pharmacy compounding done to meet individual needs.²³

The promotion of off-label uses also threatens the integrity of the new drug approval process in a basic way. If that promotion is permitted, drug manufacturers may obtain agency approval for the least risky use of the drug, and the one whose efficacy is the easiest to establish. The riskier uses with borderline efficacy, and narrow and possibly inappropriate risk/benefit ratios, can come into wide use based on a journal article with disclaimers. The Government will lose the ability to determine that the public needs to be protected by an independent agency review from the added exposure to risks from a new off-label use associated with commercial distribution of a medical article to treating physicians. FDA review is not only independent. FDA also can obtain access to all the underlying data to support claims, even those that are trade secrets. The access of medical journals to the underlying test data may be limited, however, to safeguard the manufacturer's interest in the proprietary nature of the database.²⁴

3. Obstacles to Making Disclaimers Adequate. An additional difficulty is the that providing adequate disclosures prevents obstacles that seem insurmountable. These obstacles

become clearer if one tries to envision what would make disclaimers adequate, taking into account the significance the distribution of the article by the manufacturer will have for physicians.

a. **Warning Caption.** Disclaimers, if they could be made adequate, would have to have a bluntness that those seeking them may characterize as unnecessary. This issue can be seen by examining the disclaimer identified by the Supreme Court as suitable in *Western States*. The Court found that claims not approved by FDA should be identified by a “warning” to the physician and consumer.²⁵ Use of a “warning” as the introductory signal is appropriate with respect to off-label uses, given the importance of alerting the physician to the significant responsibility that he or she is undertaking in evaluating off-label uses promoted by the manufacturer. There is likely to be resistance to such a clear signal, however. Nonetheless it should be required, and, if it is not, the manufacturer should have to provide the evidence that other captions are fully adequate to alert physicians.

b. **Distribution As Endorsement.** When a pharmaceutical company distributes a medical article reporting on off-label uses, physicians are likely to see the distribution as an endorsement, in some way, by the company of the new use as adequate to meet the standards of the profession as well as the usual testing standards for drugs. The physician may also assume that if the new use proves harmful, the manufacturer will be subject to products liability for any inadequacies in the testing or in the warnings that the manufacturer provides with the medical article on the off-label use.

In the absence of a manufacturer endorsement of the off-label use, the physician would

recognize the potential for medical malpractice liability if the new use does not meet professional standards. The physician would exercise the cautions involved in being sure that the off-label use fully meets the standards of the profession. Whether the liability of the manufacturer would replace or lessen professional liability in this setting is a difficult question, and one that FDA is not in a position to resolve. The relevant point is the physician's perception that the manufacturer's endorsement of the study can lessen the extent to which the physician will rely solely on professional assessment. Thus, a disclosure would be needed that the manufacturer's distribution is not an endorsement that the article shows that the off-label use meets the professional standards (assuming this to be the manufacturer's position).

c. Specific Differences from FDA Testing Requirements. If a disclosure system were to be used it would need to indicate the specific ways in which the off-label use did not have the testing normally required for FDA approval.²⁶ A blanket statement that the risks of the off-label use are unknown, suggested in *Western States*, is not suitable here.. The testing reported in the medical journal is likely to have identified some risks associated with the new use, and the FDA labeling for the approved use will indicate others. Instead, the difficulty will be with whether the testing in the medical article is sufficient.

An adequate disclosure in this situation also needs to be indicate more than the lack of FDA approval. Indeed the disclosure identified by the Supreme Court in *Western States* referred to the lack of FDA testing, not the lack of FDA approval.²⁷ In dealing with off-label uses promoted by the manufacturer, the physician needs the benefit of knowing how the studies found in the medical journal differ from the testing FDA requires. Individual physicians have limited time to undertake study about any gaps in the studies reported in the literature and they

and expert recognition. When that exists, the product would not need the disclaimers described here. A benefit of establishing this procedure would be to encourage manufacturers to sponsor fuller studies for off-label uses that provide the level of support and safeguards needed for GRAS/E recognition. This would be preferable than having manufacturers distribute medical journals that need extensive disclaimers.

D. Health Claims on Foods. FDA asks if different standards can be used for health claims on foods than the approach found constitutionally applicable to health claims on dietary supplements. There are reasons to believe there are differences. Dietary supplement users seek the products out and may be willing to spend more time studying a disclaimer. Foods are a necessity and shoppers have limited time to review the details of disclaimers while making selections. Consumers can lose confidence in health claims generally if preliminary and weakly-supported claims are frequently put in question by new information. The valid claims that promote healthy dietary choice should not be obscured by weak claims whose validity is continually undercut.

This need for stability and confidence about health claims led to the statutory requirement for agency approval of claims when they are supported by significant scientific agreement based on the totality of the evidence, including well-designed studies.³⁸ If FDA and Congress is to reconsider it, attention needs to be given to whether disclaimers can distinguish the claims without sufficient support from the supported ones. I continue to believe the best way to provide an adequate disclaimer would be for the unapproved claims to state that do not meet the key statutory requirement of "significant scientific agreement."³⁹ However, the *Pearson* court found this standard vague and remanded for better identification of the standard.⁴⁰ FDA

should pursue articulating the criteria for significant scientific support agreement. FDA has already recognized that the standard does not require the wide degree of consensus among experts needed for general recognition of drugs. Perhaps FDA could make clear that the standard for food health claims is met if there is majority acceptance by the leading qualified experts, which can be shown by affirmative endorsement by the leading organizations. Scientific support is especially needed in this field because the ultimate validity of the claim depends upon long-term studies and population studies that are difficult to do.⁴¹ The support of scientific experts serves as a safeguard, in the absence of full testing. Of course, further experience, and full testing, could show that the views of these experts is incorrect.⁴² Still, unless that happens, the consumer should have the benefit of knowing whether a majority of experts agree with the claim.

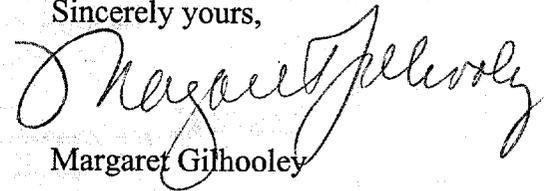
The alternative form for the disclosure should build on that used by FDA for dietary supplements on remand from the *Pearson* case. Thus it should state that FDA does not endorse the claim, but it should also state that it does not do so since there are no long-term studies to establish it, and the claim has not accepted by most experts.⁴³ A mere statement that FDA has not approved the claim could seem to reflect agency delay and inattention, so a disclaimer that reflects affirmatively FDA's non-acceptance is more informative for consumers. FDA prior review of the disclaimers should occur, as the *Pearson* court recognized was necessary for supplement claims.

E. Resources. Reviewing notifications about off-label uses and disclaimers for those claims and health claims on a timely basis places considerable demands on FDA resources. The Administration needs to consider providing additional support to enable FDA to meet its added

review and enforcement responsibilities under a constitutional scheme that relies on disclaimers rather than pre-market review to protect the public. Consideration should be given to legislation that would make those seeking to make claims based on disclaimers pay a fee to cover the added FDA staff costs. The model would be the "user fees" that must be paid by those seeking approval of new drug applications, although the fee range would be different.

F. Conclusion. The FDA Notice raised such significant and general questions that this response has had deal with the fundamental premises for regulation. I hope these comments will help illuminate the approach FDA should adopt.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Margaret Gilhooley", written in a cursive style.

Margaret Gilhooley

Professor of Law

ENDNOTES

1. 535 U.S. , 122 S. Ct. 1497 (2002)

2. See Margaret Gilhooley, *Constitutionalizing Food and Drug Law: When Avoidance Is Right*, 38 *Houston L. Rev.* 1383 (2002)(hereafter *Avoidance*), and Margaret Gilhooley, *Constitutionalizing Food and Drug Law*, 74 *Tulane L. Rev.* 815 (2000)(*Constitutionalizing*).

3. *Id.* at 1505.

4. 21 U.S.C. @ 343 (f)(need for FDA showing of a significant risk of harm) and 350b (substantiation required only for new dietary ingredients)(1994).

5. 21 U.S.C. @343 (r)(6) (1994).

6. Pub.Law 103-417, @2 (14), 108 Stat. 4326.

7. 21 U.S.C. 343(r)(6)(1994).

8. Report of Commission on Dietary Supplement Labels, Executive Summary x, and 25 (access to files and warnings on lack of safety substantiation), and Margaret Gilhooley, *Deregulation and the Administrative Role*, 62 *Montana L. Rev.* 85, 100, 110-13, and 118-19 (2001)(*Deregulation*)(discussing need to have claims be dietary in a meaningful sense and for significant scientific agreement for substantiation).

9. David F. Cavers, *The Food, Drug, and Cosmetic Act of 1938: Its Legislative History and Its Substantive Provisions*, 6 *Law & Cont. Probs.* 2 (1939).

10. *Weinberger v. Hynson*, Westcott & Dunning, 412 U.S. 609, 619 (1973)(*Hynson*).

11. *National Confectioners Ass'n v. Califano*, 569 F.2d 690, 695 (D.C. Cir. 1978).

12. 21 U.S.C. @ 352 (n)(prior review can be required only if there are "extraordinary circumstances").

13. *Western States* at 1512 .

14. *Id.* at 1507.

15. *Washington Legal Foundation (WLF) v. Henney*, 202 F. 3d 331 (D.C. Cir. 2002). See Margaret Gilhooley, *Constitutionalizing Food and Drug Law: When Avoidance Is Right*, 38 *Houston L. Rev.* 1383 (2002)(hereafter *Avoidance*).

16. *Id.* at 1505. The law allowed advertisements to consumers and doctors of the general availability of compounding services, but only if no specific drugs were identified. 21 U.S.C. @ 353a(c).
17. *Id.* at 1508. Other alternatives included banning commercial scale manufacturing equipment for compounding. *Id.* at 1506.
18. *Id.* at 1507.
19. Like *Western States*, the FDA policy has been focused on the initiation of promotion by the manufacturers and not the response to requests initiated by the user.
20. FDA's traditional policy was found in a guidance document, Advertising and Promotion; Guidances, 61 Fed. Reg. 52, 800 (1996). In *WLF v. Friedman*, 13 F. Supp. 2d 51 (D.D.C. 1998), the District Court enjoined FDA enforcement of the Guidance Document when the manufacturer distributed a reprint and disclosed the lack of FDA approval. FDA later withdrew the guidance because of the subsequent legislative enactment of FDAMA. The Court of Appeals vacated the District Court's injunction on the grounds that there was no facial restriction of speech in view of the withdrawal of the Guidance Document and the agency's interpretation of the subsequent legislation as non-mandatory. See *WLF v. Henney*, 202 F. 3d 331 (D.C. Cir. 2000).
21. 21 U.S.C.@@@360aaa (Supp. III 1997). Under that option, the manufacturer would give advance notification of the journal distribution, receive FDA comments on the disclosures needed, file a supplemental application with the agency and do additional testing after distribution of the journal article if FDA found additional tests needed.
22. See *Western States*, 122 S. Ct. at 1500-02 for a description of the concept of compounding and the statutory requirement governing compounding including the use of approved ingredients.
23. See *Western States*, at 1505.
24. PhARMA Clinical Trial Principles Restate Proprietary Rights to Protocols, Pink Sheet, p. 3-4 June 24, 2002 (reporting that PhARMA says that sponsors should not have to provide protocol information to journal editorial review groups, and that in response to requests from journals, the drug sponsor "will provide a synopsis of the clinical trial protocol and/or pre-specified plan for data analysis with the understanding that such documents are confidential and should be returned to the sponsor").
25. *Id.* at 1508.
26. Whether there need to be any separate disclosures to patients is an important matter not explored here.

27. *Western States* at 1508.

28. See Drummond Rennie, Editorial, Fourth International Congress on Peer Review in Biomedical Publication, 287 JAMA 2759, 2760 (2002)(finding that there continues to be “abundant evidence” that even with peer review “there are scarcely any bars to eventual publication”).

29. Frank Davidoff, and other editors of medical journals, Sponsorship, Authorship and Accountability, 345 NEJM 825, 826 (2001)(citing reports that unfavorable trials “may be buried rather than published”).

30. See FDA, U.S. Dep’t of Health and Human Servs., Managing the Risks from Medical Product Use, Creating a Management Framework, Report to the FDA Commissioner from the Task Force on Risk Management, 44-45 (1999).

31. The revised standards for the leading peer-reviewed journals call for authors of review articles not merely to disclose conflicts, but to have no conflicts of interest that are “significant.” Editorials, Jeffrey M. Drazen, and Gregory D. Curfman, Financial Association of Authors, 346 NEJM 1901 (2002). See Editorials, Marcia Angell, Is Academic Medicine for Sale, 342 NEJM 1516 (2002). This policy, even as modified, provides an indication of the importance of independent review, and that there are times when mere disclosure is not enough.

See Hormone Replacement Study A Shock to the Medical System, New York Times, p. A1 at A16, July 10, 2002 for a report that the book, research and lectures by the physician who was the initial supporter of the early benefits recognized for the therapy was financed by the drug manufacturer, apparently without acknowledgment.

32. See Premarket Notice Concerning Bioengineered Foods, 66 Fed. Reg. 4706 (proposed Jun. 18, 2001)(to be codified at 21 C.F.R. pts. 192, 592).

33. *Pearson v. Shalala*, 164 F.3d 650 (D.C. Cir. 1999).

34. 21 U.S.C. @ U.S.C. @@ 360aaa(c) (Supp. III 1997). See Margaret Gilhooley, Constitutionalizing Food and Drug Law: When Avoidance Is Right, 38 Houston L. Rev. 1383 (2002)(hereafter Avoidance).

35. 21 U.S.C @ 321 (p)(1994)(defining new drugs as those that are not GRAS/E).

36. 21 U.S.C. @ 321(p)(2)(1994), and Hynson, *supra* at 631-32.

37. Hynson, *supra* at 633-34.

38. 21 U.S.C. @ 343(r)(3)(A)(1994), see Constitutionalizing, at 844-51.

39. See Margaret Gilhooley, Deregulation and the Administrative Role: Looking at Dietary Supplements, 62 Montana L. Rev. 85, 110-13 (2001).

40. *Pearson*, 164 F.3d at 659-60.

41. See *Deregulation*, supra at 113-14 for a suggestion that FDA allow manufacturers to make “research in progress” claims as a way to encourage high-quality research programs.

42. A dramatic example in the case of drugs has been provided by the studies showing that estrogen replacement therapy not only fails to provide many of the benefits thought to exist but causes harm. *Hormone Replacement Study A Shock to the Medical System*, *New York Times*, p. A1, July 10, 2002. See also questioning of the role of carbohydrates and fat in the diet in *What if It’s All Been a Big Fat Lie?*, *New York Times Magazine*, p. 22 (June 7, 200).

43. See *Deregulation*, supra at 112 for disclosures used on remand.

Margaret Gilhooley

07/24/02 12:57 PM

To: fdadockets@oc.fda.gov

cc:

Subject: Request for Comments on First Amendment Issues, Docket 02N-0209

To FDA Dockets Management Branch--

I have attached my comments on the Request for Comments on First Amendment Issues, Docket 02N-0209. (I used this e-mail address since I had difficulty attaching my comments to the electronic comment address in the Federal Register).



westernstates7-24.wpd

Prof. Margaret Gilhooley

PS I am also mailing a hard copy of these comments.

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- FedEx Priority Overnight Next business morning
- FedEx Standard Overnight Next business afternoon
- FedEx First Overnight Earliest next business morning delivery to select locations
- FedEx 2Day Second business day FedEx Envelope rate not available. Minimum charge: One pound rate
- FedEx Express Saver Third business day
- NEW FedEx Extra Hours Later drop-off with next business afternoon delivery for select locations

4b Express Freight Service

- FedEx 1Day Freight* Next business day
- FedEx 2Day Freight Second business day
- FedEx 3Day Freight Third business day

* Call for Confirmation:

5 Packaging

- FedEx Envelope*
- FedEx Pak* Includes FedEx Small Pak, FedEx Large Pak, and FedEx Sturdy Pak
- Other Pkg. Includes FedEx Box, FedEx Tube, and customer pkg.

6 Special Handling

- SATURDAY Delivery Available only for FedEx Priority Overnight and FedEx 2Day to select ZIP codes
- HOLD Weekday at FedEx Location Not available for FedEx First Overnight
- HOLD Saturday at FedEx Location Available only for FedEx Priority Overnight and FedEx 2Day to select locations

Does this shipment contain dangerous goods? One box must be checked.

No Yes Shipper's Declaration required Yes Shipper's Declaration not required

Dangerous Goods (incl. Dry Ice) cannot be shipped in FedEx packaging or with FedEx Extra Hours service.

Dry Ice Dry Ice, 9 UN 1845 _____ x _____ kg

Cargo Aircraft Only

7 Payment Bill to:

- Sender Acct. No. in Section 1 will be billed.
- Recipient
- Third Party
- Credit Card
- Cash/Check
- Obtain Recip. Acct. No.

Total Packages _____ Total Weight _____ Total Charges _____

Credit Card Auth. _____

8 Release Signature

Sign to authorize delivery without obtaining signature.

Margaret Gilhooley L.M.

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