

THE WEINBERG GROUP INC.

1220 Nineteenth St, NW, Suite 300
Washington, DC 20036-2400
Phone 202.833.8077
Fax 202.833.7057
e-mail science@weinberggroup.com

WASHINGTON
NEW YORK
SAN FRANCISCO
BRUSSELS
PARIS

May 3, 2002

BY HAND DELIVERY

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1061
5630 Fishers Lane
Rockville, Maryland 20852

Re: Docket No. 02P-0170/CP 1

Dear FDA:

I am writing on behalf of Amarin Pharmaceuticals, Inc. (Amarin) in support of the Citizen Petition that Amarin filed on April 22, 2002 regarding abbreviated new drug applications (ANDAs) that have been submitted for generic pergolide mesylate formulations. The Citizen Petition has been assigned the above-referenced docket number. For the reasons set forth in the Citizen Petition and in this letter, I believe that the pergolide mesylate ANDAs raise significant public health issues that FDA should address during the review process. In particular, special attention should be paid to whether the ANDAs meaningfully demonstrate bioequivalence to the reference listed drug Permax® for all dosage strengths, and whether the ANDAs meet appropriate acceptance criteria for key pergolide mesylate degradation products. These issues present heightened review challenges because of the difficulty in measuring systemic pergolide mesylate absorption, the importance of specific dose titration under the approved labeling, and the known potential for instability of pergolide mesylate formulations.

Background and Qualifications

1. I am the Director of Biopharmaceutics in the Worldwide Health Care Product Group at THE WEINBERG GROUP INC. where I provide strategic drug development, regulatory, and litigation support. My curriculum vitae is attached as Exhibit 1.

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2. I received a B.S. degree in Pharmacy from the Massachusetts College of Pharmacy in 1972 and an M.S. in Hospital Pharmacy Administration from the Arnold and Marie Schwartz College of Pharmacy of Long Island University in 1978. I received my Ph.D. in Pharmacology from the Uniformed Services University of Health Sciences in 1991. As part of my pharmacy education, I have done extensive coursework in chemistry, including on the topics of stability and degradation.

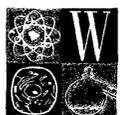
3. Prior to joining THE WEINBERG GROUP INC. I held several positions at the FDA, most recently as Director of the Division of Bioequivalence at the Office of Generic Drugs, Center for Drug Evaluation and Research (CDER). In this position I was responsible for an international program to assure that generic drugs were bioequivalent to brand name products. I further developed and contributed to drug-specific and general guidelines for the pharmaceutical industry, including such topics as *in vitro* release testing and *in vivo* bioequivalence documentation.

4. At CDER, I was also Director of the Division of Pharmacokinetics Evaluation III, Office of Clinical Pharmacology and Biopharmaceutics, where I was charged with supervising the review of the human pharmacokinetics and bioavailability section of New Drug Applications (NDAs) and pharmacokinetic/biopharmaceutic data in Investigational New Drug Applications (INDs), and contributed to the development of agency guidance documents. I further served as Deputy Director of the Office of Generic Drugs, and Acting Section Head in the Anti-Infective Group, Division of Biopharmaceutics, both at CDER. In the Division of Biopharmaceutics, I also served as Acting Branch Chief for the Scientific Support Branch, Acting Section Head for the Rapid Resolution Team, pharmacokinetic reviewer, and Special Assistant to the Acting Director. I served for two years as a biopharmaceutical analyst at the National Center for Drugs and Biologics.

5. As Deputy Director of the Office of Generic Drugs, I had oversight responsibility for chemistry issues presented in ANDAs. Prior to joining FDA, I was Deputy Chief, Assistant Chief, and Director of Quality Control in the Pharmacy Department of the United States Public Health Service Hospital in Staten Island, New York. This position, like my positions at the Office of Generic Drugs, required a knowledge of pharmaceutical chemistry. In total, I have over 30 years of experience as a pharmaceutical scientist.

6. I am a member of several professional societies, including the American Society for Clinical Pharmacology and Therapeutics (ASCPT) and the American Association of Pharmaceutical Scientists (AAPS). I was actively involved on the Challenges and New Initiatives Planning Committee for the "AAPS Workshop on Chemistry and Pharmacy Considerations During the Drug Development and Review Process." I am also a member of the Commissioned Officers Association of the United States Public Health Service (USPHS).

7. I have authored or co-authored various articles and abstracts on FDA regulation and bioequivalence testing. I also have presented numerous lectures and seminars to various national and international organizations, including on topics related to generic drug approvals.



Discussion

8. My conclusions set forth in this letter are based upon my understanding of the following facts:

a. In December 1988, FDA approved an NDA filed by Eli Lilly & Company (Lilly) for Permax (pergolide mesylate) as adjunctive treatment in the management of Parkinson's disease. The active ingredient in Permax is pergolide mesylate, an ergot derivative dopamine agonist.

b. Permax is supplied in 0.05 mg, 0.25 mg and 1.0 mg tablets, and is typically administered in divided doses three times a day. Careful titration is required to produce therapeutic effects and minimize adverse effects. Under the approved labeling for Permax, therapy is initiated with a daily dose of 0.05 mg and is gradually increased until optimal dosing is achieved.

c. The Permax approved labeling does not contain information on oral systemic bioavailability. The labeling states (p. 1) that there is not a sufficiently sensitive assay to detect the presence of the drug in plasma after administration of a single dose. The literature reflects at least two attempts to develop an assay to measure pergolide in plasma, one by Lilly and another by MDS Pharma Services. The Lilly assay is described in "Sensitive, Specific Radioimmunoassay for Quantifying Pergolide in Plasma." Clin. Chem. 1992 Oct.; 38 (1): 1975-1980.¹ The MDS Pharma Services assay is described in Proceedings of the 49th ASMS Conference on Mass Spectrometry and Allied Topics, Chicago, Illinois, May 27-31, 2001.² Based on the available information, it cannot be determined whether the assays are properly validated, appropriately sensitive, or state of the art. There is also no public indication to date that FDA has accepted an assay for use to measure pergolide bioavailability.

d. Pergolide mesylate is extensively metabolized. Two of the metabolites that have been detected are pergolide sulfoxide and pergolide sulfone. Both are known dopamine agonists in animals. Pergolide sulfoxide also appears to be somewhat more acutely toxic than the parent drug based on rodent data. According to FDA's Pharmacology and Toxicology Review of the Permax NDA (pp. 30, 32),³ the median lethal dose in mice for the sulfoxide was lower than for pergolide mesylate, and the sulfoxide was also responsible for clonic convulsions seen in mice.

¹ Exhibit 3 to the Amarin Citizen Petition.

² Exhibit 4 to the Amarin Citizen Petition.

³ Exhibit 5 to the Amarin Citizen Petition.



e. In the absence of stabilizing agents, pergolide mesylate formulations degrade upon exposure to light and air. The potential for degradation is particularly great in formulations with a high excipient to drug ratio such as the 0.05 mg tablets. One of the degradation products that is produced is pergolide sulfoxide, which is also a metabolite, as noted above. The degradation profile of pergolide mesylate formulations is described in the literature, including in *Analytical Profiles of Drug Substances and Excipients*, Vol. 21: 375-413 (Brittain, Harry G., ed. 1992).⁴

f. The addition of appropriate stabilizing agents can retard the degradation of pergolide mesylate formulations and decrease the resulting drop in potency. All dosage strengths of Permax contain the photostabilizer polyvinylpyrrolidone (povidone). Additionally, the 0.05 mg Permax tablet contains the antioxidant methionine. The effects of these stabilizers on preventing degradation are described in patents issued to Lilly.⁵

g. Teva Pharmaceuticals (Teva) and Ivax Pharmaceuticals, formerly Zenith Goldline Pharmaceuticals (Ivax), have each filed ANDAs that rely on Permax as the reference listed drug. Both ANDAs seek approval of 0.05 mg, 0.25 mg, and 1.0 mg pergolide mesylate tablets. According to the paragraph IV notices provided in connection with each ANDA,⁶ none of the generic formulations contains either the photostabilizer povidone or the antioxidant methionine. The Teva paragraph IV notice states that its formulations do not contain any excipient which performs the function of a stabilizing agent. The Ivax paragraph IV notice states that its formulations do not include any stabilizing agent such as those in the Permax formulations.⁷ An international patent application filed by Teva claims a process of manufacturing substantially stable pergolide mesylate without stabilizing additives.⁸

A. Bioequivalence Issues

9. The ANDAs that have been submitted for generic pergolide mesylate formulations must demonstrate in vivo bioequivalence to Permax in order for there to be an assurance that the generic formulations will be safe and effective and exhibit the same clinical profile as Permax. Assurances of the safety and effectiveness of Permax are provided by the

⁴ Exhibit 8 to the Amarin Citizen Petition.

⁵ Exhibits 6 and 7 to the Amarin Citizen Petition.

⁶ Exhibits 9 and 10 to the Amarin Citizen Petition.

⁷ All of these facts are derived from publicly available sources. I have not had access to the Permax NDA. Information in the NDA may bear on the matters discussed in this letter.

⁸ Exhibit 11 to the Amarin Citizen Petition.



clinical trials that support its approval and subsequent marketing experience. The same assurances will not exist for the generic pergolide mesylate formulations in the absence of in vivo bioequivalence data.

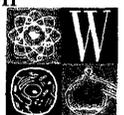
10. The need for rigorous bioequivalence data is particularly acute here because of the careful dose titration that is required for pergolide mesylate under the approved labeling. The importance of the bioequivalence showing is also heightened by the potential for degradation in the generic pergolide formulations, discussed further below. Based on the approved labeling for Permax, we know that adverse reactions may occur within the therapeutic dosage range, and that in premarketing clinical trials 27 per cent of study subjects withdrew from therapy due to an adverse event. If the bioavailability of any of the generic formulations differs from Permax in a material way, and drug is absorbed at a greater or lesser rate or extent than with Permax, safety issues could arise or effectiveness could be diminished.

11. It is important that the ANDAs demonstrate in vivo bioequivalence for *all* dosage strengths, including the 0.05 mg strength. As reflected in FDA's regulations (21 C.F.R. § 320.33(e)(5)), heightened bioequivalence issues can arise in formulations with a high excipient to drug ratio, such as the 0.05 mg tablet here. High excipient to drug ratios may result in the active drug becoming entrapped within an insoluble excipient mass and not being absorbed. Furthermore, it is possible that with drug products with high excipient to active drug ratios, the assay of combined tablets (10 to 20) may be within compendial limits, while the drug content of individual tablets may far exceed these limits in both positive and negative directions. Here, the 0.05 mg is especially important because it is the starting dose and integral to the dose titration called for by the Permax labeling.

12. While we have assurances of the safety and effectiveness of all the Permax dosage strengths from the clinical trials conducted to support approval and from marketing experience, we have no equivalent assurance for the different generic dosage strengths without an appropriate bioequivalence showing. It would be inappropriate to permit the ANDA applicants to extrapolate bioequivalence for the 0.05 mg tablet from a showing of bioequivalence on either the 0.25 mg or 1.0 mg tablets, or otherwise to waive the bioequivalence requirement for any of the dosage strengths.

13. Although the need for bioequivalence data to support approval of the ANDAs for generic pergolide formulations is great, there does not appear to be an established assay that has been accepted by FDA for measuring pergolide levels in human plasma. This creates special review issues.

a. The Permax labeling states that "information on oral systemic bioavailability of pergolide mesylate is unavailable because of the lack of a sufficiently sensitive assay to detect the drug after the administration of a single dose." The only data available in the labeling on the absorption of pergolide mesylate are from tests involving ¹⁴C radiolabeled pergolide mesylate in which some but not all of the administered pergolide radioactivity was recovered. While such tests suggest that a significant portion



of the drug is absorbed, they do not provide evidence of the rate and extent of absorption of the drug and thus do not provide a basis for establishing bioequivalence.

b. According to publicly available FDA review documents, Lilly committed to continue development work on an assay in connection with the Permax approval. The literature indicates that Lilly and others have indeed undertaken to develop such an assay, as discussed further above, but there is no indication that this work has yielded a validated and state-of-the art assay that is adequately sensitive to measure absorption for the different dosage strengths involved.

14. It is unclear how the pergolide ANDA applicants can make the bioequivalence showing that is required because of the apparent lack of an accepted assay for measuring bioavailability. This showing is fundamental for the reasons set forth above. Put simply, the public health could be put at risk if generic formulations are introduced that differ significantly in rate or extent of drug absorption from the reference listed drug upon which the generic approvals would rest. This concern must be resolved before approving the ANDAs.

15. The need for a showing of bioequivalence as to the pergolide metabolites should also be considered. At least two of the known metabolites -- the sulfoxide and the sulfone -- are understood to be dopamine agonists in animals and thus have apparent pharmacologic activity. One of those metabolites -- the sulfoxide -- was shown in mice studies to be more acutely toxic than the parent drug. If an assay is developed to measure pergolide absorption, and these metabolites are shown to form presystemically, then bioequivalence should also be required as to the metabolites. Bioequivalence of the parent drug does not guarantee bioequivalence of metabolites when there is presystemic metabolite formation.

B. Degradation and Stability

16. Pergolide mesylate formulations become unstable and degrade when exposed to light and air, resulting in a demonstrable drop in the potency. This can occur during the manufacturing process.

17. The potential for degradation is particularly marked in tablets with a large excipient to drug ratio such as the 0.05 mg tablet, which contains approximately 50 mcg pergolide in a tablet of 300 mg total weight. The active drug is overwhelmed by the amount of excipients, especially when one or more excipients have some activity in degrading the active.

18. One of the primary degradation products formed is pergolide sulfoxide, which is also a pergolide metabolite. As discussed above, the sulfoxide product has apparent pharmacologic activity and potentially greater toxicity than the parent drug. Accordingly, the presence of inappropriate levels of pergolide sulfoxide would present safety concerns.



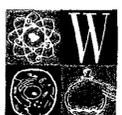
19. This potential for degradation can be addressed by the addition of appropriate stabilizers in the pergolide formulation. For example, all of the Permax formulations contain the photostabilizer povidone, and the 0.05 mg Permax tablet contains the antioxidant methionine.

20. Teva stated in its paragraph IV notice that its pergolide formulations contain no stabilizers. Ivax stated in its paragraph IV notice that its pergolide formulations do not contain stabilizers equivalent to those in the Permax formulations. These statements raise important questions that must be answered in the review process about the levels of degradation products seen in the generic formulations, including in particular in the important 0.05 mg tablets, which are key to proper dosing.

21. It is critical that the ANDAs establish and meet appropriate acceptance criteria for pergolide sulfoxide. This is specified in FDA's *Draft Guidance for Industry: Impurities in Drug Products* 6 (Dec. 1998), and it is important as a matter of public health to ensure that unsafe levels of the sulfoxide are not produced by degradation of the generic formulations.

22. Photostability should also be considered for all of the different proposed generic dosage strengths. FDA's *Draft Guidance for Industry: Stability Testing of Drug Substances and Drug Products* 62-63 (1998) states that photostability must be addressed where exposure to light produces a potential stability issue and application is being made for a new product formulation. These circumstances exist here. We know that pergolide formulations degrade upon exposure to light, yet Teva's paragraph IV notice that its products contain no photostabilizer, and Ivax's notice states that its products do not contain an equivalent photostabilizer to Permax. The generic formulations thus present clear potential photostability issues that must be assessed and resolved.

23. Any lack of stability in the generic formulations due to the absence of appropriate stabilizers would of course also need to be taken into account in fixing the expiration dating.



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As explained above and in the Amarin Citizen Petition, the Teva and Ivax ANDAs raise important review issues related to bioequivalence, degradation, and stability. It is important as a matter of public health that these issues be answered in a scientifically sound manner before the ANDAs are approved.

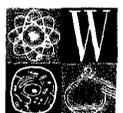
Respectfully submitted,



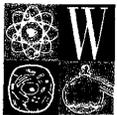
Nicholas M. Fleischer, R.Ph., Ph.D.
Director of Biopharmaceutics
THE WEINBERG GROUP INC.

Encl.

cc: Gary J. Buehler, Director, Office of Generic Drugs



**EXHIBIT 1:
CURRICULUM VITAE
NICHOLAS M. FLEISCHER, Ph.D.**



NICHOLAS M. FLEISCHER, Ph.D.

EDUCATION

- | | |
|------|---|
| 1991 | Ph.D., Pharmacology, Uniformed Services University of the Health Sciences, Bethesda, Maryland |
| 1978 | M.S., Hospital Pharmacy Administration, Arnold and Marie Schwartz College of Pharmacy of Long Island University, Brooklyn, New York |
| 1972 | B.S., Pharmacy, Massachusetts College of Pharmacy, Boston, Massachusetts |

EXPERIENCE

Dr. Fleischer joined THE WEINBERG GROUP INC. in 1997 as the Director of Biopharmaceutics in the Worldwide Health Care Products Group. He has 29 years of experience in biopharmaceutics, pharmacokinetics, clinical pharmacology and pharmacy. Prior to joining THE WEINBERG GROUP, Dr. Fleischer held several positions at the United States Food and Drug Administration (FDA), the most recent being Director of the Division of Bioequivalence, Office of Generic Drugs, Center for Drug Evaluation and Research (CDER). At CDER, he was also Director of the Division of Pharmaceutical Evaluation III, Office of Clinical Pharmacology and Biopharmaceutics, Chief of the Pharmacokinetics Evaluation Branch I, Division of Biopharmaceutics, Deputy Director in the Office of Generic Drugs, and Acting Section Head in the Anti-Infective Group, Division of Biopharmaceutics. In the Division of Biopharmaceutics, he also served as Acting Branch Chief for the Scientific Support Branch, Acting Section Head for the Rapid Resolution Team, pharmacokinetic reviewer, and Special Assistant to the Acting Director. He served for 2 years as a biopharmaceutical analyst at the National Center for Drugs and Biologics.

Prior to joining the FDA, Dr. Fleischer was Deputy Chief, Assistant Chief, and Director of Quality Control in the Pharmacy Department of the United States Public Health Service Hospital, Staten Island, New York. He maintains his clinical practice of pharmacy on a part-time basis. His experience at THE WEINBERG GROUP includes:

Strategic, Drug Development, and Regulatory Support

- Provides evaluation and analysis of a product development plans for pharmaceuticals and biologics, providing strategic direction based on regulatory, scientific, and marketing issues
- Contributes to or direct due diligence evaluations for potential acquisitions, including consideration of scientific data and possible regulatory strategies
- Evaluates and provided advice to clients on adequacy of draft regulatory submissions; manages revisions of pharmacology, clinical, toxicology, and manufacturing sections as needed



- Provides scientific and strategic support to client in resolving product effectiveness and/or safety issues, including thorough review and critical analysis of the published literature pertaining to the drug class.

Litigation support

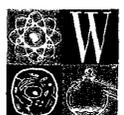
- Serves as an expert witness in generic drug and pharmaceutical patent infringement litigation.

Prior to joining THE WEINBERG GROUP, Dr. Fleischer's FDA experience included the following:

Director, Division of Bioequivalence, Office of Generic Drugs, CDER, FDA. Responsible for an international program to assure that generic drugs were bioequivalent to the brand name products. Directed approximately 24 doctoral level scientists in the review of the bioequivalence section of generic drug applications. Established sound scientific principles and promoted their application in a consistent and fair manner. Developed and contributed to drug-specific and general guidelines for the pharmaceutical industry including SUPAC-SS Nonsterile Semisolid Dosage Forms Scale-up and Postapproval Change: Chemistry, Manufacturing, and Controls; *In Vitro* Release Testing and *In Vivo* Bioequivalence Documentation.

Director, Division of Pharmaceutical Evaluation III, Office of Clinical Pharmacology and Biopharmaceutics, CDER, FDA. Responsible for supervising the review of the human pharmacokinetics and bioavailability section of New Drug Applications (NDAs) and pharmacokinetic/biopharmaceutic data in Investigational New Drug Applications (INDs). The first three anti-HIV protease inhibitor drugs were reviewed and approved under his directorship. Dr. Fleischer served as the first chairman of the Biopharmaceutics Coordinating Committee and chaired the Therapeutics Inequivalence Action Coordinating Committee. He contributed to the development of the following guidance's:

- Guidance for Industry: Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies *In Vitro* (I).
- Dissolution Testing of Immediate Release Solid Oral Dosage Forms
- Extended-Release Solid Oral Dosage Forms and Development, Evaluation, and Application of *In Vitro-In Vivo* Correlations



Significant Review Activities

- Identified potential polymorphic metabolism of omeprazole, first proton-pump inhibitor
- Uncovered problems with Bolar's generic version of Dyazide, which led to major recall and legal action against Bolar and subsequent Congressional investigation of FDA's generic drug approval process
- Developed market-wide remedial plan to prevent moisture-related decrease in bioavailability of carbamazepine tablets.

PROFESSIONAL AFFILIATIONS

American Society for Clinical Pharmacology and Therapeutics (ASCPT)
American Association of Pharmaceutical Scientists (AAPS)
European Federation for Pharmaceutical Sciences (EUFEPS)
AAPS Workshop on Bioequivalence of Topical Dermatological Dosage Forms Planning Committee
AAPS Workshop on Chemistry and Pharmacy Considerations During the Drug Development and Review Process: Challenges and New Initiatives Planning Committee
Commissioned Officers Association of the USPHS
Massachusetts College of Pharmacy Alumni Association
Rho Chi Pharmaceutical Honor Society

HONORS AND AWARDS

Center for Drug Evaluation and Research Special Recognition Award, 5 June 1998 (2 awards)
Meritorious Service Medal, U.S. Public Health Service, 30 May 1991
Graduate Student Grant for Research, USUHS, November 1987 and November 1986
Emma L. Bockman Award, USUHS, 13 May 1987
Unit Commendation, U.S. Public Health Service, 29 September 1981
Achievement Medal, U.S. Public Health Service, 12 August 1981



LANGUAGES

Fluent in Hungarian

PUBLICATIONS

Falk, J. and Fleischer, N. 1998. FDA Modernisation Efforts. The Regulatory Affairs Journal. July:469-471.

Shah, V., Flynn, G., Yacobi, A., et al. 1998. AAPS/FDA Workshop Report: Bioequivalence of Topical Dermatological Dosage Forms -- Methods of Evaluation of Bioequivalence. Pharm. Res. 15(2):167-171.

Singh, G.J., Fleischer, N., Lesko, L., and Williams, R. 1998. Evaluation of the Proposed FDA Pilot Dose-Response Methodology for Topical Corticosteroid Bioequivalence Testing. Pharm. Res. 15(1):4-7.

Malinowski, H., Marroum, P., Uppoor, U.R., et al. 1997. Draft Guidance for Industry, Extended-Release Solid Oral Dosage Forms and Development, Evaluation, and Application of *In Vitro-In Vivo* Correlations. Adv. Exp. Med. Biol. 423:269-288.

Zelonis, A., Fleischer, N., and Walling, R. 1979. A pharmacy quality assurance program. Hospital Pharmacy.

Fleischer, N. 1973. Promethazine hydrochloride-morphine sulfate incompatibility. Am. J. Hosp. Pharm. 30(8):665.

ABSTRACTS

Fleischer, N. 2001. Clinical Pharmacology Perspectives of Recent FDA Bioequivalence Decisions. Poster at the 2001 Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics, 6-10 April, Orlando, FL. (Abstract published in Clin. Pharm. Ther. 69(2):P36).

Fleischer, N. 1998. Bioequivalence - Past, Present and Future. European Journal of Pharmaceutical Sciences 6/Suppl.1:S98.

Conner, D., Roizen, M., Fleischer, N., Almirez, R., and Peck, C. 1989. Transcutaneous Chemical Collection of Isoflurane in Surgical Patients. Poster at the International Conference on Prediction of Percutaneous Penetration, 4-6 April, Manchester, United Kingdom, (Abstract published in Pharmacotherapy 9(3):777).



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Fleischer, N. and Peck, C. 1988. Formulation of the Gaseous Anesthetic Isoflurane for Intravenous Injection. Poster at the NIH/ADAMHA-Industry Collaboration Forum, 25 October, Washington, DC, the FDA Science Poster Exposition, 27-28 April, Rockville, Maryland, and the Annual Meeting of the American Association of Pharmaceutical Scientists, Washington, DC, 2 November, 1986, (Abstract published in *Pharmaceutical Research* 3(5):91S, 1986).

Fleischer, N., Peck, C., et al. 1988. Reduced Cutaneous Blood Flow Affects Transdermal Chemical Migration. Poster at the FDA Science Poster Exposition, Rockville, Maryland, 27-28 April, and at the Annual Meeting of the American Society of Clinical Pharmacology and Therapeutics, 9-11 March, San Diego, California. (Abstract published in *Clin. Pharm. Ther.* 43(2):137, 1986).

Fleischer, N. and Peck, C. 1988. The Transdermal Collection of Intravenously Administered Isoflurane. Poster at the FDA Science Poster Exposition, 27-28 April, Rockville, Maryland, and the Graduate Research Colloquium of the Uniformed Services University of the Health Sciences, 13 May, 1987, Bethesda, Maryland. Also presented at the Department of Pharmacology Seminar, USUHS, 28 April, 1987, and the Graduate Student Symposium of the DC Section, Society for Experimental Biology and Medicine, 25 March, Bethesda, Maryland, (Abstract published in *Proc. Soc. Exp. Biol. Med.* 188(1):115, 1988).

Fleischer, N., Peck, C., et al. 1988. The Pharmacokinetics of Intravenously Administered Isoflurane in the Rat. Poster at the FDA Science Poster Exposition, 27-28 April, Rockville, Maryland, and The Annual Meeting of the American Association of Pharmaceutical Scientists, 2-6 November, 1986, Washington, DC, (Abstract published in *Pharmaceutical Research* 3(5):165S, 1986).

Peck, C., Conner, D., Fleischer, N., et al. 1987. Physiologically Based Pharmacokinetic Modeling of Noninvasive Transcutaneous Chemical Dosimetry. Presented by N. Fleischer, at the Hanford Life Sciences Symposium, 20-23 October, Richland, Washington, (Abstract published in *Health Physics*, 57(Suppl.):157, 1989).

TEACHING

Fleischer, N. 2001. The Full NDA. Presented at the Food and Drug Law Institute Workshop on Introduction to Drug law and Regulation: Understanding How the FDA Regulates the Drug Industry, 8 November, Washington, DC

Fleischer, N. 2000. The Full NDA. Presented at the Food and Drug Law Institute Workshop on Introduction to Drug law and Regulation: Understanding How the FDA Regulates the Drug Industry, 14 September, Washington, DC



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Fleischer, N. 2000. International Regulatory Systems: Operating in a Global Market - ICH, FDA Initiatives, Reality. Presented at the Food and Drug Law Institute's 2000 Summer Internship Program. 21 June, Washington, DC.

Fleischer, N. 1999. The Full NDA. Presented at the Food and Drug Law Institute Workshop on Introduction to Drug Law and Regulation: Understanding How FDA Regulates the Drug Industry, 4 November, Washington, DC.

Fleischer, N. 1998. Marketing Exclusivity: Selected Current Issues Facing Generic and Innovator Drug Companies - Scientific Perspectives. Presented at the Food and Drug Law Institute's 42nd Annual Education Conference, 17 December, Washington, DC.

Fleischer, N. 1998. The Full NDA. Presented at the Food and Drug Law Institute Course on Introduction to Drug Law and Regulation, 5 November, Washington, DC.

Fleischer, N. 1998. (initial appointment, 1993). Adjunct Associate Professor, Department of Pharmacology, Division of Clinical Pharmacology, Uniformed Services University of the Health Sciences, Bethesda, Maryland.

Fleischer, N. 1997. The "New Drug" Approval Requirement. Presented at the Food and Drug Law Institute Course on Introduction to Drug Law and Regulation, 27 October, Washington, DC.

Fleischer, N. 1997. Career Options for Ph.Ds. Presented at York College, CUNY, 29 September, Queens, New York.

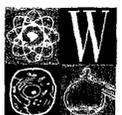
Fleischer, N. 1990. Decisions in the Approval Process for ANDA's. Presented at the Advanced New Drug Approval Training for Analysts, 27 September, Philadelphia, Pennsylvania.

Fleischer, N. 1990. Monitoring Generic Drugs: An FDA Update and Perspective. Presented at the 35th Annual Ohio Pharmaceutical Seminar, 18 April, Columbus, Ohio.

Fleischer, N. 1989. Biopharmaceutical Issues. Presented at the Continuing Education Seminar for Federal Pharmacists, 9 December, Bethesda, Maryland.

Fleischer, N. 1989. MK-Model: A Demonstration. Presented at Division of Biopharmaceutics Scientific Rounds, 3 February, Rockville, Maryland.

Fleischer, N. 1979. Invited lecturer on "Pharmacy Practice in the USPHS and Career Opportunities," Rutgers College of Pharmacy, December 1979 and November 1980, Piscataway, New Jersey.



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Fleischer, N. 1979. Invited lecturer on "Pharmacists in the Federal Government," Rutgers College of Pharmacy, March 1979, Piscataway, New Jersey.

Fleischer, N. 1977. Invited lecturer on "Aseptic Technique in Intravenous Additive Manufacture and Incompatibilities," USPHS Hospital Medical Intensive Care Unit Course for Nurses, January 1979 and March 1977.

Fleischer, N. 1977 and 1973. Invited lecturer for Pharmacology, Physician Assistant Training Program, USPHS Hospital, Staten Island, New York.

Fleischer, N. 1974. Invited lecturer for Pharmaceutical Calculations, Physician Assistant Training Program, USPHS Hospital, Staten Island, New York.

PRESENTATIONS

Fleischer, N. 2001. Evaluating the Present Position on Generic Biologics. Presented at the Institute for International Research meeting on Preparing for Successful Submissions & Understanding the Legal Challenges to Expedite Market Entry, 4 December, McLean, VA.

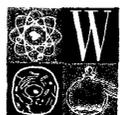
Fleischer, N. 1999. For Which Drug Products is a Multiple-Dose Bioequivalence Study Necessary. Presented at the Institute for International Research meeting on Establishing Bioequivalence - Speeding Development and Meeting Regulatory Requirements, 18 June, Philadelphia, PA.

Fleischer, N. 1999. International Regulatory Guidelines: Where We Have Been and Where We Are Going. Presented at the Institute for International Research meeting on Establishing Bioequivalence - Speeding Development and Meeting Regulatory Requirements, 17 June, Philadelphia, PA.

Fleischer, N. 1998. Generic Drugs and Intellectual Property Rights in the Global Pharmaceutical Market - FDA Perspectives. Presented at the Fourth European Congress of Pharmaceutical Sciences, 11 September, Milan, Italy.

Fleischer, N. 1998. What Will the Requirements for Individual Bioequivalence Studies Mean for Generic Registrations in Europe. Presented at the Institute for International Research conference on Achieving Successful Generic Product Registration under the New System in Europe, 14 July and 2 April, London, England.

Fleischer, N. 1998. Utilizing Bioequivalence Study Requirements to Speed-Up Development and FDA Approval. Presented at the Institute for International Research conference on Generics - Marketing, Compliance & Procurement Strategies to Maximize Your Competitive Edge, 26 February, Orlando, Florida.



Fleischer, N. 1997. Update on Streamlining Bioequivalence Review Process, Database for Bio-Reviews. Presented at the 1997 Mid-Year Meeting and Educational Conference of the National Association of Pharmaceutical Manufacturers, 23 June, Washington, DC.

Fleischer, N. 1997. Division of Bioequivalence Perspectives. Presented at the 1997 Generic Pharmaceutical Industry Association Annual Meeting, 10 March, Miami, Florida.

Fleischer, N. 1997. Initiatives for Division of Bioequivalence. Presented at the 1997 National Association of Pharmaceutical Manufacturers Annual Meeting, 31 January, Naples, Florida.

Fleischer, N. 1996. Regulatory Perspectives of Product Line Extensions. Presented at the AAPS Midwest Regional Meeting, 20 May, Chicago, Illinois.

Fleischer, N. 1994. Penetration Enhancers -- Current Status, Regulatory and Safety Aspects. Presented at the AAPS Ninth Annual Meeting and Exposition, 8 November, San Diego, California.

Fleischer, N. 1993. Biopharmaceutics Perspectives in Drug Development. Presented at the AAPS Workshop on Chemistry and Pharmacy Considerations During the Drug Development and Review Process: Challenges and New Initiatives, 23 September, Arlington, Virginia.

Fleischer, N. 1990. Generic Drugs: Changes Being Implemented. Presented at the 86th Annual Meeting of the National Association of Boards of Pharmacy, 20 May, Phoenix, Arizona.

Fleischer, N. 1990. Safety and Efficacy in the Generic Drug Industry. Presented at the Annual Conference of the National Council for Prescription Drug Programs, 15 February, Scottsdale, Arizona.

Fleischer, N. 1989. FDA Commentary on Drug Metabolism Section of NDA. Presented at the Drug Development Workshop of the Regulatory Affairs Professionals Society, 13 June, Bethesda, Maryland.

Fleischer, N. 1989. New Programs in the Division of Biopharmaceutics. Presented at the 28th Annual International Industrial Pharmacy Conference, 2 June, Austin, Texas.

Fleischer, N. 1989. Importance of Pharmacokinetics/Pharmacodynamics in the Drug Development Process. Presented at the PMA R&D/Medical Section Annual Meeting, 12 April, Laguna Niguel, California.

Fleischer, N. and Peck, C. 1988. Utilization of Physiologic Pharmacokinetic Modeling to Evaluate the Transdermal Efflux of Isoflurane. Presented at the Second Annual Symposium Frontiers of Pharmacokinetics and Pharmacodynamics, 12-14 October, Little Rock, Arkansas.



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Fleischer, N. 1986. Disposition and Transdermal Collection of Isoflurane. Presented at the Graduate Research Colloquium, USUHS, 14 May, Bethesda, Maryland, and at the Department of Pharmacology Seminar, USUHS, 6 May, Bethesda, Maryland.

Zelonis, A., Fleischer, N., and Walling, R. 1978. A Pharmacy Quality Assurance Program. Presented by A. Zelonis, at the USPHS Professional Association Meeting, 28 March, Atlanta, Georgia.

Fleischer, N. and Zelonis, A. 1977. Pharmacist Involvement at an Oncology Clinic. Presented by A. Zelonis, at the USPHS Professional Association Meeting, 6 April, San Francisco, California.

Fleischer, N. 1975. Improved Utilization of Pharmacy Manpower, by N. Fleischer. Presented (by title only) at the USPHS Professional Association Meeting, 2-5 June, Las Vegas, Nevada.

Fleischer, N. 1974. Quality Control for Microbial Contamination in a Hospital Pharmacy. Presented at the USPHS Professional Association Meeting, 9 April, Washington, DC.

Fleischer, N. 1973. Invited speaker on "Pharmacy as a Profession," Egbert Junior High School, Staten Island, April, New York.

