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10 AMERICAN HOME PRODUCTS CORPORATION and
WYETH-AYERST LABORATORIES COMPANY

11 SUPERIOR COURT OF THE STATE OF CALIFORNIA
12 FOR THE COUNTY OF LOS ANGELES – SOUTHEAST DISTRICT
13

14 KATHY TIFFITH and SHERRI SHARP,) J.C.C.P. 4032
15)
Plaintiffs,) DD Nos. 718 (Sharp); 572 (Tiffith)
16 v.)
17 MANHATTAN WEIGHT CONTROL, et al.,) DECLARATION OF PRAVIN M.
Defendants.) SHAH, M.D. IN SUPPORT OF
18) OPPOSITION OF AHP TO MOTION
19) FOR CLASS CERTIFICATION AND
AND RELATED CROSS-ACTION.) PREFERENTIAL TRIAL SETTING
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28)

DATE: AUGUST 13, 1999
TIME: 10:00 A.M.
DEPT.: SE-D

DECLARATION OF PRAVIN M. SHAH, M.D.

I, Pravin M. Shah, M.D. declare as follows:

1. I am a cardiologist, the Medical Director of the Hoag Heart Institute, Newport Beach, California and am a Professor of Medicine at Loma Linda University Medical Center, located in Loma Linda, California. I have personal knowledge of the facts set forth herein, and if called as a witness I could and would testify competently thereto under oath.

2. As described in greater detail in my curriculum vitae, an accurate copy of which is attached as Exhibit A, my medical career has focused on the diagnosis and treatment of patients with cardiopulmonary problems. I am the Chair of the International Committee of the American College of Cardiology, and a member of the Editorial Board of the Journal of the American College of Cardiology. I am also an Editor of the Journal of Heart Valve Disease, which has an international circulation. I previously served on the Board of Directors of the American Society of Echocardiography, and as President of the Los Angeles Society of Echocardiography.

3. I directed Loma Linda's cardiology training program from 1987 until June 1998. I previously held the position of Professor of Medicine at the University of California, Los Angeles (1977-1987) and the University of Rochester, New York (1975-1977), in addition to other professorial positions in cardiology and pediatrics. I also served as Chief of the Cardiology Section, West Los Angeles VA Medical Center, Wadsworth Division (1977-1985).

4. I was a member of the Committee on Clinical Application of Echocardiography which developed the most recent ACC/AHA Guidelines for the Clinical Application of Echocardiography, which were approved by the American College of Cardiology Board of Trustees in October 1996 and by the American Heart Association Science Advisory and Coordinating Committee in December 1996, and which were published in Circulation and the Journal of the American College of Cardiology.

1 the valve at the time of closing can be detected. In fact, the majority of normal subjects have some
2 “trace” or “mild” valvular regurgitation in at least one of their heart valves, as assessed by
3 echocardiography. These subjects generally require no medical treatment. This low level of
4 regurgitation is consistent with completely normal heart valve function, and is not a symptom or
5 precursor of heart disease. In other words, the existence of detectable regurgitation does not
6 necessarily demonstrate valvular abnormality.

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8 12. More serious valve abnormalities can result from a variety of causes, including
9 congenital, inflammatory, degenerative, ischemic, functional and “idiopathic” (unknown)
10 conditions. The following conditions, unrelated to diet drug use, are known causes of regurgitation
11 at the aortic and mitral valve at varying degrees of severity:

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13 **Mechanisms and Etiologies of Chronic Mitral Regurgitation**

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Mechanism	Condition
Inflammatory	Rheumatic heart disease Systemic lupus erythematosus Takayasu’s arteritis Scleroderma Rheumatoid arthritis Carcinoid heart disease Methysergide and ergotamine therapy
Degenerative	Myxomatous degeneration of mitral valve leaflets Mitral valve annular calcification Ehlers-Danlos syndrome Pseudoxanthoma elasticum
Infectious	Bacterial endocarditis
Structural	Ruptured chordae tendineae

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1 **Mechanisms and Etiologies of Chronic Mitral Regurgitation**

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Mechanism	Condition
	Dilation of the mitral valve annulus Hypertrophic cardiomyopathy Paravalvular prosthetic leak
Ischemia	Rupture or dysfunction of the papillary muscles Coronary artery disease Acute ischemia Chronic ischemia
Congenital	Mitral valve clefts or fenestrations Parachute mitral valve abnormality Marfan's syndrome

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Mechanisms and Etiologies of Chronic Aortic Regurgitation

Mechanism	Condition
Inflammatory	Rheumatic fever Syphilis Systemic lupus erythematosus Ankylosing spondylitis Reiter's syndrome Behcet's syndrome Takayasu's arteritis Carcinoid heart disease Methysergide and ergotamine therapy
Structural	Annular dilation from aortic aneurysm Sinus of valsalva aneurysm Fenestrated valve
Infectious	Bacterial endocarditis
Disruptive	Trauma Aortic dissection
Congenital	Marfan's syndrome Ventricular septal defect Pseudoxanthoma elasticum Osteogenesis imperfecta Mucopolysaccharidoses Ehlers-Danlos syndrome Unicuspid, bicuspid, quadricuspid valves

Mechanisms and Etiologies of Chronic Aortic Regurgitation

Mechanism	Condition
Degenerative	Aging/degenerative calcification Hypertension Renal failure

13. Heart valve structure and function are also affected simply by the aging process, therefore, higher levels of valvular regurgitation are naturally found in older people. Such regurgitation is thus found in many otherwise normal subjects -- that is, patients with no clinically evident heart disease.

14. Thus, a given individual's risk of developing a valvular abnormality, or "valvulopathy," depends upon many unique factors such as the individual's age, medical history, and family history, among others. Additionally, to diagnose the etiology, or cause, of abnormal valvular regurgitation requires individualized inquiry into whether or not the patient has one of the many medical conditions described above. The appropriate treatment, including monitoring (if any), will depend on the results of that individualized inquiry.

Echocardiographic Techniques

15. Over the past few years, echocardiographic equipment and techniques have become more sensitive and sophisticated, such that trivial amounts of valve regurgitation can be detected. Trivial regurgitation is not associated with heart murmurs, and in fact represents a normal finding.

16. Until the early 1980s, the technology used for echocardiograms consisted of a two dimensional, black-and-white sonographic image. While this technology allowed echocardiographers to visualize the principal structures of the heart and detect significant malformations, it was not possible to visualize the flow of blood with much clarity.

1 17. In the early 1980s, echocardiographers began to employ a color Doppler technology
2 that, by computer enhancement, produces images in which blood flowing in one direction is coded
3 with one color, while blood flowing in an opposite direction is coded with an entirely different
4 color. (A similar technology is used in television weather forecasts where storms of varying
5 severity and speed are assigned different colors by a computer.)

6 18. The color Doppler technology allows echocardiographers to assess valvular
7 regurgitation. As a result, it has now been determined that many normal patients have some
8 valvular regurgitation, even though that subtle degree of regurgitation is not accompanied by a heart
9 murmur and has no clinical relevance.

10 19. The classification of severity of valvular regurgitation, in turn, is subject to varying
11 interpretations. Some echocardiographers measure the size of the regurgitant jet -- that is, the color
12 imprint of the velocity of blood entering the receiving chamber. This approach has led to
13 considerable inconsistency, because variations in gain settings (the volume at which the sound wave
14 which creates the image is set), transducer frequency, and the make of equipment can in turn vary
15 the size of the regurgitant jet's image as it appears in the echocardiogram.

16 20. Other variations in echocardiographic evaluation occur because there is no consensus
17 in describing the results. Like most other techniques (e.g., angiography), echocardiography is only
18 semiquantitative in assessing the severity of valve regurgitation. Two different systems are used: a
19 numeric scale using grades one through four, and a descriptive scale using the grades "trace" (also
20 called "trivial" or "physiologic"), "mild," "moderate," and "severe." The correspondence between
21 the two grading systems is not standardized. Some observers will translate a finding of "trivial" or
22 "trace" regurgitation into "grade 1." Others will not assign a numeric grade to that level of
23 regurgitation because it is considered normal, and will translate a finding of "mild" regurgitation
24 into "grade 1." Thus a "grade 2" assessment by one echocardiographer may indicate "moderate"
25 regurgitation because it is considered normal, and will translate a finding of "mild" regurgitation
26 into "grade 1." Thus a "grade 2" assessment by one echocardiographer may indicate "moderate"
27 regurgitation because it is considered normal, and will translate a finding of "mild" regurgitation
28 into "grade 1." Thus a "grade 2" assessment by one echocardiographer may indicate "moderate"

1 regurgitation, while the same numeric grade by another may indicate only “mild” regurgitation. No
2 objective criteria have been established to differentiate between trace and mild regurgitation.

3 21. A significant percentage of clinically normal patients, without any disease or medical
4 problems, have evidence of regurgitation, when an echocardiogram is performed, particularly when
5 modern color Doppler technology is used in the assessment. For example, in 1992, Drs. Lavie,
6 Hebert, and Cassidy published a study in which they used color Doppler echocardiography to assess
7 the prevalence and severity of regurgitation at the mitral and aortic valves of 206 patients, all of
8 whom had previously been classified as normal based on the absence of any structural abnormality
9 of the heart on their echocardiograms. In that particular study, which focused on a group of patients
10 aged 15 to 86 (mean 47), the investigators found the following percentages for various categories of
11 mitral and aortic regurgitation:
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Type of Regurgitation	Percent
<u>Mitral</u>	
None	27
Trivial	27
Mild	40
Moderate	6
Severe	0
<u>Aortic</u>	
None	88
Trivial	5
Mild	5
Moderate	2
Severe	0

1 22. The Lavie study also concluded that regurgitation in otherwise normal hearts was
2 related to age. Specifically, the study found that the prevalence of moderate mitral regurgitation
3 was three to four times greater in people 50 or older than among people younger than 50. Similarly,
4 aortic regurgitation was more than twice as likely (17% v. 7%) in patients 50 or older than in those
5 younger than 50, in the absence of any structural abnormality of the aortic valve.

6 23. There are a number of other studies which have measured levels of valvular
7 regurgitation via echocardiograms. These studies likewise demonstrate that valvular regurgitation
8 at one or more heart valve is not an uncommon finding, and that the prevalence of such
9 regurgitation increases as patients age.

10 24. More recently, as a result of studies conducted on patients who took fenfluramine or
11 dexfenfluramine, we have additional information regarding the prevalence of valvular regurgitation.
12 A number of those studies have compared the prevalence of valvular regurgitation in matched
13 controls to those who took fenfluramine or dexfenfluramine. This means that an effort was made to
14 identify patients with characteristics similar to those of patients who took fenfluramine or
15 dexfenfluramine (e.g., age and weight), but who had not taken fenfluramine or dexfenfluramine,
16 and to perform echocardiograms on those patients as well as the treated patients, all of which were
17 read in a blinded fashion. In my opinion, depending on the quality of the study, these data regarding
18 the control populations are the most relevant in terms of considering a base-line prevalence of
19 valvular regurgitation in patients who took fenfluramine or dexfenfluramine. Likewise, in my
20 opinion, also depending on the quality of the study, these data are the most relevant in terms of
21 determining whether or not there is an increased prevalence of valvular regurgitation in patients
22 who took fenfluramine or dexfenfluramine. Collections of data which lack blinding or controls are
23 subject to too many biases to be reliable.
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1 regurgitation or other signs or symptoms of cardiovascular disease, no further procedures or tests
2 are medically indicated.

3 28. In his declaration, plaintiff's expert witness Dr. Samuel Sobol states that clinical
4 examinations are often inadequate to detect abnormal valvular regurgitation. However, the study he
5 relies upon by Rahko, *Prevalence of Regurgitant Murmurs in Patients with Valvular Regurgitation*
6 *Detected by Doppler Echocardiography*, *Annals of Internal Med.* 1989;111:466-472, compared the
7 ability to detect any level of valvular regurgitation using pulsed-Doppler echocardiography with
8 that detected solely by auscultation. As explained above, the pulsed-Doppler echocardiography
9 used for this comparison predated the advent of color Doppler technology, and it was shown by the
10 study to have a greater tendency to both overestimate the presence of valvular regurgitation and
11 miss abnormalities detected by auscultation. It is for this reason that the pulsed-Doppler method for
12 evaluation of valve regurgitation has been totally abandoned in clinical practice. Notably, the
13 Rahko study relied upon only one clinical method, auscultation, to detect regurgitation. In practice,
14 however, clinical examinations are not limited to auscultation to detect valvular regurgitation, as
15 physicians ask patients for various clinical symptoms and check their heart impulse and blood
16 pressure. Even with this limitation, however, the Rahko study shows that the ability of physicians
17 to detect clinically significant valvular regurgitation through auscultation alone is high.

18 29. As a general rule, it is not standard medical practice to screen or monitor via
19 echocardiograms patients who are at an increased risk of developing valvular regurgitation in the
20 absence of physical signs or symptoms. For example, although patients with histories of rheumatic
21 fever are at an increased risk of developing cardiac valve abnormalities, it is not standard medical
22 practice to screen such patients for those abnormalities through performing routine echocardiograms
23 in the absence of symptoms or signs suggestive of heart disease. Likewise, although age is
24 associated with an increased prevalence of valvular regurgitation, older patients are not screened or
25 monitored for the development of such regurgitation through echocardiograms.

1 30. I understand that Dr. Sobol has testified, as a justification for en masse
2 echocardiographic screening, a concern that mild valvular regurgitation may otherwise go
3 undetected. Although it may be true that mild forms of valvular regurgitation may not be detectable
4 through a clinical examination, if the valvular disease reaches a level of clinical significance it is
5 detectable through such a clinical examination. Echocardiograms are not necessary to identify
6 patients with valvular heart disease of sufficient severity to require medical intervention or
7 treatment.
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9 31. The inappropriateness of screening patients without signs or symptoms of valvular
10 heart disease has been stated by the American Heart Association (“AHA”) and the American
11 College of Cardiology (“ACC”) generally as to all patients, and specifically with regard to patients
12 who have taken fenfluramine or dexfenfluramine.

13 32. Practice guidelines developed by the ACC and AHA establish that in the absence of
14 signs (e.g., an audible murmur) or symptoms of cardiovascular disease, or in rare instances a family
15 history supporting a possibility of valvular heart disease, an echocardiogram should not be
16 performed on the patient merely for reassurance of either the physician or the patient, or for some
17 other reason not specified in the ACC/AHA Guidelines. American College of
18 Cardiology/American Heart Association Task Force on Practice Guidelines, Circulation, Vol. 95,
19 No. 6 (March 18, 1997) (“ACC/AHA Guidelines”). I was a member of the Committee that
20 developed these guidelines, and as I recall, the Committee was unanimous on this recommendation.
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22 33. Indeed, the ACC/AHA Guidelines counsel against indiscriminant use of
23 echocardiography. In addition to the cost factor, mass screening via echocardiographic examination
24 creates the possibility of inappropriate treatment by doctors that could be harmful to the patient:
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26 “Indiscriminant use of echocardiography or its use for ‘screening’ is
27 not indicated for two principal reasons. First, the cost of
28 echocardiography is not trivial. Second, the current Doppler
echocardiographic techniques reveal details of structure and function
such as . . . jet velocities representing minimal and at times transient

1 valvular insufficiency [regurgitation] that could generate unnecessary
2 further testing or inappropriate and potentially detrimental therapy.”

3 ACC/AHA Guidelines at page 1690.

4 34. Furthermore, a finding of trivial or mild regurgitation upon echocardiogram can
5 generate anxiety in patients and lead to unnecessary changes in lifestyle and unnecessary treatment,
6 even though the finding is not clinically significant.

7 35. As a result of recent reports of valvular heart disease occurring in patients who used
8 fenfluramine and/or dexfenfluramine, the AHA and ACC specifically addressed the appropriate
9 monitoring of such patients in recent guidelines published in November 1998. ACC/AHA
10 Guidelines for the Management of Patients With Valvular Heart Disease: A Report of the American
11 College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee
12 on Management of Patients with Valvular Heart Disease) J. Am. Coll. Cardiol. 1998; 32: 1486-588
13 (“ACC/AHA Guidelines Re: Valvular Heart Disease”). As stated therein, the ACC and AHA
14 emphasize the importance of clinical judgment, stating, “it is not possible to derive definitive
15 diagnostic and treatment guidelines for patients who received these anorectic drugs. Hence, clinical
16 judgment is important.” Id. at 1540. These leading professional organizations go on to state:
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18 “In light of the current evidence, echocardiographic screening of all
19 patients with a history of fenfluramine or dexfenfluramine use,
20 especially asymptomatic patients without associated findings, is not
21 recommended.” (Id.)

22 36. In arriving at these guidelines which counsel against general echocardiographic
23 screening, the AHA and ACC expressly considered and took note of published data regarding a
24 possible association between the taking of anorectic agents and valvular heart disease, including:
25 (1) Connolly, H.M.; Crary, J.L.; McGoon, et al. Valvular Heart Disease Associated With
26 Fenfluramine-Phentermine. New Eng J Med 1997; 337:581-588 (“Connolly Article”); (2) Center
27 for Drug Evaluation and Research. Food and Drug Administration Web Site. FDA analysis of
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1 cardiac valvular dysfunction with use of appetite suppressants. Available at:
2 <http://www.fda.gov/cdernews> (“FDA Analysis”); (3) Khan, et al., The Prevalence of Cardiac
3 Valvular Insufficiency Assessed By Transthoracic Echocardiography In Obese Patients Treated
4 With Appetite-Suppressant Drugs, *New Eng. J. Med.*, Vol. 339, No. 11 (September 10, 1998), 713-
5 718 (“Khan Study”); (4) Weissman, et al., An Assessment of Heart-Valve Abnormalities In Obese
6 Patients Taking Dexfenfluramine, Sustained Release Dexfenfluramine, or Placebo, *New Eng. J.*
7 *Med.*, Vol. 339, No. 11 (September 10, 1998), 725-731 (“Weissman Study”); and (5) Jick, et al., A
8 Population Based Study of Appetite-Suppressant Drugs and the Risk of Cardiac-Valve
9 Regurgitation, *New Eng. J. Med.*, Vol. 339, No. 11 (September 10, 1998), 719-724 (“Jick Study”).

11 37. In those guidelines the ACC and AHA also took note of and explained their
12 interpretation of interim guidelines published by the Department of Health and Human Services a
13 year earlier, before publication of the Weissman, Jick or Khan Studies. Specifically, on November
14 13, 1997 the DHHS made the following recommendations with respect to patients who took
15 fenfluramine or dexfenfluramine: (a) that fenfluramine and dexfenfluramine users should
16 individually consult their physicians; (b) that if such users show signs or symptoms of heart or lung
17 disease, they should have an echocardiogram; (c) that physicians should strongly consider having
18 echocardiograms performed when certain invasive medical procedures are being planned; but (d)
19 that the ultimate decision as to whether or not this is the prudent course rests with the physician,
20 based upon his or her evaluation of each individual patient.

22 38. With regard to the DHHS Recommendations the AHA and ACC stated:

24 “The Committee on Management of Patients With Valvular Heart
25 Disease adopted the majority of the DHHS recommendations.
26 However, the committee recommends that certain DHHS statements
27 remain open to interpretation by individual physicians because of the
28 lack of conclusive scientific data for appropriate care of patients who
have taken these drugs. Specifically, the committee interprets the
DHHS statement that practitioners should “strongly consider”
performing echocardiography on all persons before they undergo
invasive procedures, such as dental procedures, regardless of whether

1 42. Thus, there is no clear scientifically supported benefit in identifying mild valvular
2 regurgitation in patients with no signs or symptoms of valvular heart disease so that they can be
3 prescribed antibiotic prophylaxis before dental treatments (or for any other reason). Moreover,
4 there are potential harms posed by such an indiscriminant program. Antibiotics, like all drugs, carry
5 risks, including the risk of death from anaphylactic shock.

6 43. Just as the clinical examination is the accepted practice for screening for valvular
7 heart disease, it is the appropriate method for following patients with known valvular abnormalities.
8 Thus, for example, patients with known damage to their heart valves as result of rheumatic fever, or
9 congenital defects such as bicuspid aortic valves (aortic valves usually have three leaflets, a
10 relatively common congenital abnormality is when the aortic valve has two leaflets, bicuspid), are
11 followed clinically, not through multiple echocardiograms. Only if a patient's medical condition
12 changes should any medical testing or intervention be applied, and then the appropriate medical
13 testing or intervention utilized should be determined on an individualized basis, depending upon the
14 changes in the patient's condition and pre-existing medical condition.

15 44. I understand that Dr. Sobol has testified that one of the reasons in his opinion for
16 screening echocardiograms for all, and multiple echocardiograms for those with mild valvular
17 regurgitation, is to provide information regarding the natural history of valvular regurgitation
18 caused by the ingestion of fenfluramine or dexfenfluramine. In my opinion the program
19 recommended by Dr. Sobol is unlikely to derive this result, and it is not likely to have any direct
20 benefit to the vast majority of subjects who would undergo testing. I believe that such
21 indiscriminate testing would result in anxiety, inappropriate interpretations and potential for harm to
22 the patient. In my judgment, such a program should be structured as a research protocol and
23 deemed scientifically sound, and should only be undertaken with the approval by the appropriate
24 "Institutional Review Committee for Human Research" and with the informed consent of the
25 patients.

1
2 **There Is No Basis for Deviating From Standard Medical Practice In The**
3 **Treatment of Patients Who Took Fenfluramine or Dexfenfluramine**

4 45. The scientific studies conducted to date indicate that it is likely that there are
5 significant differences among patients in terms of their possible risk of developing valvular
6 regurgitation, depending on duration, dose and possibly combination use. There are no data
7 suggesting latency, and recent data indicate that if there is an association between the taking of
8 fenfluramine or dexfenfluramine and the development of valvular regurgitation it is unlikely to
9 progress, and may regress.

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12 **Connolly Article**

13 46. The Connolly Article was published in August 1997, and reported on the authors'
14 observation of valvular abnormalities considered to be unique in 24 patients who had taken
15 fenfluramine in combination with phentermine for an average duration of 11 months. Contrary to
16 plaintiffs' purported concern for asymptomatic patients, all 24 of those patients had signs and/or
17 symptoms of valvular heart disease. As noted by the authors of the Connolly Article, these
18 observations supported further scientific inquiry, but did not establish even an association between
19 the taking of fenfluramine and phentermine and the development of the observed valvular
20 abnormalities. The Connolly Article provides no guidance regarding the possible prevalence of the
21 observed valvular abnormalities — since the size of the patient population from which the 24
22 patients reported upon were drawn from is unknown, it is impossible to determine a denominator or
23 to calculate prevalence from such data.
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FDA Survey And Spontaneous Reports

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2 47. Following publication of the Connolly Article, the FDA received data from five diet
3 centers regarding the prevalence of valvular regurgitation found in patients who took primarily
4 fenfluramine in combination with phentermine, (271 of the 291 patients), for an average of 14
5 months (the “FDA Survey Data”). These data are described in the FDA Analysis cited earlier in
6 this declaration, and in the CDC Morbidity and Mortality Weekly Report, November 14, 1997, Vol.
7 No. 46, No. 45, pp.1061-1066 (“MMWR”).
8

9 48. The patients described in the FDA Survey Data were assessed via echocardiograms.
10 The FDA adopted a “case definition” of mild or greater aortic regurgitation and/or moderate or
11 greater mitral regurgitation with regard to this echocardiographic data and the spontaneous reports
12 described below. In selecting this case definition the FDA noted that lesser degrees of regurgitation
13 are relatively common in the general population and are not generally considered abnormal.
14 MMWR at 1061. Although this case definition is helpful in distinguishing “background noise”
15 (highly prevalent levels of valve regurgitation) it does not equate with clinical significance. Thus,
16 for example, mild aortic regurgitation detected via an echocardiogram, absent a clear structural
17 abnormality, is considered a normal variant and is generally ignored in clinical practice.
18

19 49. The FDA Survey Data indicated an increased prevalence of mild or greater aortic
20 regurgitation or moderate or greater mitral regurgitation. However, the gathering of these data
21 lacked any scientific controls. Specifically, the data was gathered without blinding or controls,
22 meaning that the people who took the echocardiograms and interpreted them knew that the patients
23 being assessed had taken fenfluramine in combination with phentermine, and that this was the
24 reason they were undergoing an echocardiogram. As noted above, the interpretation of
25 echocardiograms is semi-quantitative, and, without scientific and technical controls, gathering data
26 in this manner renders the findings suspect. There is also an issue of selection bias with regard to
27 these data. For example, Dr. Richard Bowen — the doctor who contributed the greatest number of
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1 patients in the survey — has publicly stated in the Wall Street Journal that some of his patients were
2 specifically selected because they had murmurs or symptoms of cardiac disease. The symptom-
3 based selection method described by Dr. Bowen would have artificially inflated the observed
4 prevalence of valvular regurgitation.

5 50. In addition to this survey data, the FDA reported on spontaneous reports of heart
6 valve abnormalities found in patients who took fenfluramine and/or dexfenfluramine. MMWR at
7 1061. Among the millions of people who took these drugs, the FDA cited 113 reports that met the
8 case definition. These reports were primarily with regard to patients who had taken fenfluramine in
9 combination with phentermine (79%) and the median duration of use was 9 months. It is difficult to
10 draw any conclusions from these data, firstly because spontaneous reports involve no assessment of
11 causality, and thus they at most mean that a heart valve abnormality was found in a patient who
12 took one of the drugs in question. Moreover, these data provide no guidance as to the prevalence,
13 since “the denominator” — that is, the number of people who took the drugs over all the years in
14 question — is unknown (although it is reportedly in the range of 5 to 6 million).
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17 51. Following the publication of these data, efforts were undertaken to study
18 scientifically the question of whether patients who took fenfluramine or dexfenfluramine are at an
19 increased risk of developing heart valve abnormalities, and to quantify that risk (if any). Three
20 studies seeking to answer these questions were published in the New England Journal of Medicine
21 on September 10, 1998 — the Weissman, Khan and Jick Studies. Taken together these studies
22 indicate that any risk of developing heart valve regurgitation is far less than originally suggested
23 and is affected by duration, dose and possibly combination use.
24

25 **The Weissman Study**

26 52. The Weissman Study evaluated patients who took dexfenfluramine alone for a
27 median duration of 78 days. That study showed no statistically significant differences in the
28 prevalence of valvular regurgitation in treated versus untreated patients according to the FDA case

1 definition. Thus, the Weissman Study indicates that patients who took dexfenfluramine for short
2 durations are not at an increased risk of developing valvular regurgitation at that level.

3 **The Khan Study**

4 53. The Khan Study involved comparisons of echocardiograms of patients who took
5 fenfluramine in combination with phentermine, dexfenfluramine alone, and dexfenfluramine in
6 combination with phentermine. The Khan Study did not describe any increased prevalence of
7 moderate or greater mitral regurgitation. The Khan Study did report higher prevalences of mild or
8 greater aortic regurgitation but these prevalences varied depending on the drugs used and the
9 duration: (1) 26.3% in patients who took fenfluramine in combination with phentermine for an
10 average duration of 26.5 months; (2) 24.5% in patients who took dexfenfluramine in combination
11 with phentermine for 9 months, and (3) 12.7% in patients who took dexfenfluramine alone for an
12 average duration of 4.9 months. Thus, it appears that duration is an important factor in these results
13 and possibly combination use. And the Khan Study provides no data with respect to patients who
14 took the drugs for three months or less.
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17 54. Methodological questions regarding the Khan Study bear some mention. Although
18 the Khan Study described the concordance between readers as high, this is generally because there
19 was good agreement in the “none” category where the vast majority of findings were found. In
20 categories of trace, mild, moderate and severe regurgitation the variability between observers is
21 considerable. However, the authors fail to discuss this point. It also appears that a wide variety of
22 machines were used, and this use of differing technology can skew results. Finally, the inclusion of
23 sixty echocardiograms previously read in an unblinded fashion is a potential source of bias.
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26 **The Jick Study**

27 55. The Weissman and Khan Studies, and most of the data available, address valvular
28 regurgitation detected by echocardiograms, and not valvular disease of clinical significance. The

1 Jick Study attempted to study valvular regurgitation in a different manner. The Jick Study involved
2 an analysis of medical records over a period of five years for more than 8,900 patients who had
3 been treated with dexfenfluramine or fenfluramine in Great Britain (where the nature of the medical
4 practice permits comprehensive review of all records for a given patient). Dr. Jick reported that
5 these records indicated the apparent development of aortic and/or mitral valve regurgitation (of
6 some unspecified degree), which could not be explained by other preexisting conditions such as
7 rheumatic fever or congenital heart disease that can independently produce such regurgitation, in
8 only 11 of the 8,900 patients. The severity of valvular regurgitation present in the patients
9 described in the Jick Study cannot be determined. Although 8 of the 11 patients had
10 echocardiograms, the Jick Study does not report on the findings of the echocardiograms. As to the
11 other 3 patients, 2 had clinical diagnoses, and the third apparently simply filled out a questionnaire.
12

13 56. The dose of fenfluramine for some of the patients in Dr. Jick's study was twice the
14 standard dose in the United States. But the most significant aspect of Dr. Jick's study is the finding
15 of only 11 patients with heart valve regurgitation that was not otherwise explainable out of more
16 than 8,900 patients who took fenfluramine or dexfenfluramine. There appeared to be a duration or
17 dose related component to the findings, with patients who took fenfluramine or dexfenfluramine for
18 four months or longer having a higher incidence of valvular abnormalities than patients who took
19 the drugs for shorter periods of time. Even among patients who took the drugs for four months or
20 longer, however, the appearance of valvular abnormalities was rare (less than 1 in 1000 per year).
21

22
23 **The Combined Impact of the**
24 **Weissman, Khan and Jick Studies**

25 57. The Weissman and Jick Studies indicate that the likely prevalence of any type of
26 valvular abnormality that will be associated with dexfenfluramine or fenfluramine will be far lower
27 than previously reported -- especially in patients who took the drugs for relatively short periods.
28 While the Khan Study showed higher prevalences than the Weissman or Jick Studies (although still

1 lower than initial reports), the Khan Study also indicates that duration is a factor and possibly
2 combination use.

3 **The Gardin Study**

4 58. On November 11, 1998, a study conducted by Dr. Julius M. Gardin of the University
5 of California, Irvine was presented at the annual meeting of the American Heart Association
6 (“AHA”) (the “Gardin Study”). The Gardin Study involved patients who had taken fenfluramine in
7 combination with phentermine (n=455), dexfenfluramine (n=479) and matched controls (n=539).
8 The Gardin Study found no difference between the treated and untreated groups with regard to
9 serious cardiovascular events, including no cases of endocarditis among the nearly 1,000 treated
10 patients. The only statistically significant finding at the FDA case definition level was with regard
11 to mild or greater aortic regurgitation, and this finding was limited to patients who had taken the
12 drugs three months or more. Moreover, even as to this finding of statistical significance, most of
13 the regurgitation was mild.
14
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16 **The Shively Study**

17 59. A similar study was conducted and presented at the November 1998 AHA annual
18 meeting by Dr. Bruce Shively of Oregon Health Sciences University (“the Shively Study”). The
19 Shively Study involved only dexfenfluramine. The Shively Study had results similar to the Gardin
20 Study — the only statistically significant difference between treated and untreated patients was with
21 regard to mild or greater aortic regurgitation; most of this was mild, and even this occurred only if
22 the drug was taken more than three months.
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25 **The Davidoff Study**

26 60. On December 10, 1998, at a meeting of EUROECHO held in Trieste, Italy, Dr.
27 Ravin Davidoff of Boston University Medical Center presented the findings of a study comparing
28 the echocardiograms and cardiovascular evaluations of a group of patients who took fenfluramine

1 alone for approximately three months to those of patients who took placebos. (“the Davidoff
2 Study”). The Davidoff Study involved echocardiographic and cardiovascular assessments on
3 patients who had participated approximately four years earlier in a study conducted by the Fred
4 Hutchinson Cancer Research Center in Seattle on smoking cessation. The 530 participants in the
5 Davidoff Study had either taken placebo or fenfluramine alone as part of the smoking cessation
6 trial.

7
8 61. The Davidoff Study found no statistically increased prevalence of valvular
9 regurgitation or cardiovascular findings in the treated group versus the untreated group. These
10 results are consistent with the findings of the Weissman and Gardin Studies that short term use is
11 not associated with increased prevalences of valvular regurgitation. These results may also indicate
12 that to the extent any such increased prevalence existed during the time the fenfluramine was being
13 taken, or shortly thereafter, this increased prevalence disappeared over time. Finally, given the
14 four-year period between the time the drugs were taken and the time the echocardiographic
15 evaluation was made, the Davidoff Study is strong evidence that any valvulopathy from these drugs
16 is not latent and does not progress.
17

18 19 **The Ryan Study**

20 62. More recently, on March 9, 1999, Dr. Thomas Ryan, Associate Professor of
21 Medicine and Director of Echocardiography of Duke University presented initial findings of the
22 largest echocardiographic study to date regarding patients who had taken fenfluramine in
23 combination with phentermine. These data were presented at the annual meeting of the ACC.
24

25 63. Like the Gardin and Davidoff Studies, the Ryan Study showed no statistically
26 increased prevalence of valvular regurgitation in patients who took fenfluramine for shorter periods
27 of time. Indeed, the Ryan Study showed no statistically increased prevalence of FDA case
28 definition valvular regurgitation for patients who took fenfluramine in combination with

1 phentermine for less than six months. With respect to patients who took this combination for longer
2 periods of time, the only statistically significant difference at the FDA case definition level was
3 with respect to mild or greater aortic regurgitation.

4 Natural History

5 64. There is no evidence that the mild levels of valvular regurgitation found in some of
6 the foregoing studies progress after discontinuation of drug therapy. Recent data indicate that this
7 mild regurgitation, even if present, does not progress and may even regress.

8 65. As noted above, the Weissman Study reported that there was no increased prevalence
9 of FDA case definition valvular regurgitation in patients treated with dexfenfluramine as compared
10 to those who had taken placebos. The patients in the Weissman Study had been enrolled in a
11 clinical trial of a new sustained release form of dexfenfluramine. Accordingly, there were two
12 treatment groups: one group took dexfenfluramine and the other took the sustained release form.
13 When both treatment groups and all levels of valvular regurgitation were combined, including trace
14 aortic regurgitation, and physiologic and mild mitral regurgitation, there was statistical significance,
15 due primarily to higher levels of physiologic, trace or mild regurgitation in the treatment groups.

16 66. An abstract presented at the June 1999 meeting of the American Society of
17 Echocardiography (“ASE”) reported on follow-up echocardiograms performed on these same
18 patients. Weissman, Neil, J., M.D., et al., Does the Increased Prevalence of Regurgitation
19 Associated with Appetite Suppressants Persist 3-5 Months After Discontinuation of Medication?,
20 Journal of the American Society of Echocardiography, v. 12(5), 1999 (“Weissman II”).
21 Weissman II found that the increased prevalence of valvular regurgitation when treatment groups
22 and all levels of regurgitation were combined had disappeared. These data indicate the absence of
23 progression and the possibility of regression.

24 67. Also presented at the June 1999 meeting of the ASE was an abstract authored by
25 James P. Eichelberger, M.D., and others, regarding echocardiographic findings of valvular
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1 regurgitation in patients who had participated in an earlier study of the “fen-phen” combination. 15
2 Year Outcome Data On Patients Treated With Fenfluramine/Phentermine Combination, Journal of
3 the American Society of Echocardiography, v. 12 (5), 1999 (“Eichelberger Study”). That initial
4 study, which commenced in 1983, was a blinded and randomized crossover trial sponsored by NIH,
5 the purpose of which was to determine the efficacy of the combination of fenfluramine and
6 phentermine in losing weight. Dr. Eichelberger and his colleagues evaluated, via echocardiograms,
7 83 of the 121 patients who had participated in that prior study. They found the prevalence and
8 severity of valvular regurgitation in these patients, 15 years after their exposure to fenfluramine in
9 combination with phentermine, to be similar to the prevalence reported in patients with recent
10 exposure. Dr. Eichelberger and his colleagues concluded that these data suggest a lack of
11 significant regression or progression of valvular regurgitation over this 15 year period of time.
12 They also found that although few of the patients with valvular regurgitation had been prescribed
13 antibiotic prophylaxis, none had developed endocarditis. Further, no patients developed heart
14 failure requiring hospitalization or the need for valve surgery. Thus, these data indicate that
15 although mild valvular regurgitation may be associated with the taking of these drugs, that
16 regurgitation is relatively stable and is not associated with more serious cardiovascular events.
17

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19 68. These recent data are also supported by the Davidoff Study which showed no higher
20 rate of FDA case definition valvular regurgitation in treated versus untreated patients four years
21 after the drugs were used.

22
23 69. Despite these studies, Dr. Sobol asserts that both aortic and mitral regurgitation are
24 progressive diseases at all degrees of severity. None of the studies Dr. Sobol relies upon indicate
25 any clinically significant progression of the levels of regurgitation. In Padiyal, et al., *Doppler*
26 *Echocardiographic Assessment of Progression of Aortic Regurgitation*, American J. of Cardiology,
27 1997;80:306-314, the authors noted only miniscule changes in the size of the left ventricle (i.e., 1
28 millimeter increase for the mild regurgitation group). Indeed, this “size” change is so small that it is

1 within the margin of error for echocardiography. This cannot be taken to indicate an increase in
2 severity in mild regurgitation, notwithstanding the authors' assertions. In Reimold, et al.,
3 *Progressive Enlargement of the Regurgitant Orifice in Patients with Chronic Aortic Regurgitation*,
4 *J of the Am. Soc'y of Echocardiography*, 1998;11:259-265, the authors noted only a "nonsignificant
5 trend" for the regurgitant volume to increase over time." Moreover, seventeen percent of the
6 patients enrolled in the Reimold study had abnormal, bicuspid aortic valves, a disease state known
7 to progress. The abstract by Raichlen, et al., *Risk Factors for Progression of Mild and Moderate*
8 *Mitral Regurgitation*, *J. of the Am. Soc'y of Echocardiography*, May 1998 at 536, focused only on
9 the factors that could cause mild or moderate mitral regurgitation to progress; it did not address
10 patients like those involved in this case with otherwise normal mitral valves.

12 70. The concept of "regurgitation begets regurgitation" applies predominantly to
13 clinically significant mitral regurgitation that is severe enough to result in enlargement of the heart
14 chambers. Progression of milder regurgitation is dependent on the underlying abnormality of the
15 heart valve itself. For example, bicuspid aortic valve regurgitation may progress with time as would
16 degenerative valve disease which commonly occurs with aging.

19 **Pulmonary Hypertension**

20 71. Over the course of my career I have treated in excess of 1,000 patients with
21 pulmonary hypertension and more than 50 patients with the more unusual condition known as
22 primary pulmonary hypertension. It is not unusual for a cardiologist, rather than a pulmonologist,
23 to treat a pulmonary hypertension patient.

25 72. I understand that the plaintiffs may also be seeking echocardiographic screening of
26 patients who took fenfluramine or dexfenfluramine in order to detect primary pulmonary
27 hypertension in these patients, without regard to whether or not these patients have any signs or
28 symptoms of that disease.

1 73. In order to address this request, it is important first to understand what this disease is
2 and then how it is diagnosed and treated. Primary pulmonary hypertension comes within the
3 broader umbrella of a condition known as pulmonary hypertension. Pulmonary hypertension is a
4 lung disorder in which the pressure in the pulmonary artery (the blood vessel that leads from the
5 heart to the lungs) rises above normal levels, making it difficult to oxygenate the blood.

6 74. Usually pulmonary hypertension develops as a result of or, as we say, is “secondary”
7 to some other medical condition. Among the causes of pulmonary hypertension are the following:
8

- 9 • Congenital heart defects such as ventricular septal defect and arterial septal defect.
- 10 • Valvular and myocardial heart disease.
- 11 • Obstructive airways diseases such as emphysema, chronic bronchitis or
12 chronic obstructive pulmonary disease.
- 13 • Parenchymal lung disease.
- 14 • Sleep apnea and obesity hypoventilation. (These conditions, which tend to
15 occur more frequently in the obese population, make it difficult for someone
16 to breathe and often are characterized by waking up at night due to the
17 inability to breathe).
- 18 • Congenital abnormalities of the lungs, thorax and diaphragm.
- 19 • Thromboembolic disease or obstruction of pulmonary vessels. These
20 include:
 - 21 Pulmonary thromboembolism.
 - 22 Mediastinal Fibrosis.
 - 23 Congenital stenosis.
 - 24 Foreign bodies, i.e., talc.
 - 25 Tumor.
 - 26 Hemoglobinopathies (disorders of red blood cells such as sickle cell
27 anemia).
 - 28 Schistosome eggs.
- Autoimmune and collagen vascular diseases such as lupus, scleroderma and HIV.
- Pulmonary vasculitides.
- Portal hypertension.

- 1 • Cirrhosis.
- 2 • Exogenous substances, which include L-Tryptophan and crack cocaine
- 3 ingestion among others.
- 4 • Living at a high altitude.

5 75. Pulmonary hypertension can also exist without any apparent cause. Thus, when all
6 of the above known potential causes of pulmonary hypertension are ruled out by appropriate testing,
7 a determination can be made that the pulmonary hypertension is “primary” -- hence the
8 nomenclature “primary pulmonary hypertension (“PPH”).”

9 76. Primary pulmonary hypertension is an extremely rare disease and affects about 1-2
10 people out of every million of the general population. Generally speaking, primary pulmonary
11 hypertension is a disease of young women. Women are about twice as likely to contract PPH than
12 men, with most developing it in their thirties or forties.

14 77. The mere fact that a patient who took fenfluramine, dexfenfluramine or phentermine
15 develops pulmonary hypertension does not mean that the drug was the cause. As with any patient
16 with pulmonary hypertension, all other known causes would have to be ruled out before such a
17 hypothesis could be generated. Even if a known cause of pulmonary hypertension is not identified,
18 it is possible that the individual is one of the few who will develop pulmonary hypertension for no
19 apparent reason, irrespective of his or her ingestion of the drugs in question. To determine the
20 cause of a particular patient’s pulmonary hypertension, if that is possible at all, a physician would
21 need to examine each individual patient’s medical history. A physical examination and various
22 diagnostic tests would have to be performed to consider the many possible causes. The approach to
23 diagnosis and then to treatment and monitoring, if any, would vary significantly depending upon the
24 patient’s symptoms, medical history and current condition.

25 78. The International Primary Pulmonary Hypertension Study (IPPHS) is the only
26 epidemiological study that has studied a possible association between the taking of fenfluramine,
27
28

1 dextfenfluramine and other anti-obesity medications and the development of PPH. According to the
2 International Primary Pulmonary Hypertension Study (IPPHS), Abenheim, L., et al., *Appetite-*
3 *Suppressant Drugs and the Risk of Primary Pulmonary Hypertension*, New Eng. J. Med.
4 1996;335:609, the risk of PPH among patients who used anti-obesity medications for three months
5 or less is no different than for the general population. The IPPHS did not study patients who had
6 taken the drug aminorex, which I understand was referred to by Dr. Sobol in his deposition.
7 Aminorex was off the market many years before the IPPHS. There is no comparison between
8 aminorex and the drugs studied in the IPPHS – the association between aminorex and the
9 development of PPH is orders of magnitude greater than the association found in the IPPHS with
10 regard to the diet medications that it studied.
11

12 79. Assuming that the conclusions of the IPPHS are correct, the risk reported in the
13 IPPHS of patients who took any of the diet drugs studied developing PPH remains exceedingly rare.
14 The IPPHS also found that the risk of developing PPH differed significantly depending upon how
15 long an individual used those anti-obesity medications, and that among patients who took such
16 medications for 3 months or less, the risk of developing PPH was not statistically different than for
17 the general population. Even as to those patients found to be at some increased risk in the IPPHS
18 (those who took the drugs for more than three months), the risk remains very rare — about 23 to 46
19 out of a million, or between 1/20,000 and 1/40,000.
20

21 80. With regard to patients who had ceased taking diet drugs for one year or longer, the
22 IPPHS found that such patients do not face a statistically increased risk of developing primary
23 pulmonary hypertension — if they have not developed symptoms of that disease within that first
24 year after they ceased taking diet medications, there is no medical or scientific reason for believing
25 that they will later develop this disease as a result of taking those medications. Here the diet
26 medications in question, fenfluramine and dexfenfluramine, have been off of the market for close to
27 two years (since September 1997), and accordingly asymptomatic patients who took these
28

1 medications are at no known increased risk of developing PPH.

2 81. Indeed, the Gardin, Davidoff and Ryan Studies all evaluated pulmonary hypertension
3 as well as valvular regurgitation in the treated and untreated populations. These studies found no
4 statistically increased prevalence of elevated pulmonary artery pressures in patients who took
5 fenfluramine and/or dexfenfluramine.

6 82. Based on my knowledge and experience as a physician, it is my opinion that the kind
7 of medical surveillance, if any, needed to detect PPH in patients who took fenfluramine or
8 dexfenfluramine depends on many individual circumstances. For example, whether or not the
9 patient has symptoms of PPH, if the patient took the drugs in question for what length of time, what
10 other drugs or medical conditions are part of the patient's medical history, and what other medical
11 regimes are indicated for the patient based on medical conditions independent of PPH.
12

13 83. Furthermore, based on my knowledge and experience as a physician, it is my opinion
14 that medical surveillance to detect PPH in asymptomatic patients who took fenfluramine or
15 dexfenfluramine via echocardiographic screening is not medically sound. As noted above,
16 according to the IPPHS the increased incidence of this disease in patients who took a variety of diet
17 medications for more than three months is only 23-46 out of a million.
18

19 84. Moreover, since a diagnosis of PPH is really one of exclusion, the "screening"
20 sought by plaintiffs would not focus on that specific disease, but rather on detecting the more
21 general, much more common, medical condition of pulmonary hypertension secondary to another,
22 diagnosable medical condition, such as those listed above.
23

24 85. Thus, the appropriate medical approach is to follow up, when medically indicated, on
25 patients who present signs or symptoms of pulmonary hypertension. What should be done with
26 regard to that follow-up depends upon patient specific factors, including the signs or symptoms
27 presented, and the patient's medical history.
28

1 **The Class Representatives**

2 **Kathy Tiffith**

3 86. I understand that plaintiff Kathy Tiffith is a 46 year old woman who testified at her
4 deposition that took a combination of fenfluramine and phentermine intermittently from sometime
5 in 1990 or 1991 to approximately July 1997. I have reviewed Ms. Tiffith's medical records,
6 including the results of an echocardiogram performed in October 1997. The records indicate that
7 Ms. Tiffith suffers from anemia, chronic bronchitis, chest pains and probable COPD, none of which
8 are related to her ingestion of diet drugs. The Echocardiogram Doppler Report dated November 6,
9 1997 states as follows: "Essentially normal echocardiographic study with evidence of normal
10 systolic function and there is no evidence of valvular abnormalities."
11

12 87. Based on clinical evaluation as well as the normal findings of her 1997
13 echocardiogram, it is my opinion that Ms. Tiffith does not need any special medical monitoring for
14 possible injuries caused by her ingestion of fenfluramine and/or phentermine. In my opinion, there
15 is no evidence that suggests any abnormality with Ms. Tiffith's heart.
16

17 **Sherri Sharp**

18 88. I understand that plaintiff Sherri Sharp is a 38 year old woman who took a
19 combination of fenfluramine and phentermine from December 1996 to approximately April 1997. I
20 have reviewed Ms. Sharp's medical records, which indicate that she suffers from various conditions
21 which predate her ingestion of diet drugs, including heart palpitations, intermittent dyspepsia,
22 allergic bronchitis, asthma, elevated blood pressure and obesity. I understand that, after taking the
23 drugs, Ms. Sharp has been examined repeatedly by her physicians, and such examinations have
24 included auscultation of the heart. I further understand that Ms. Sharp has recently undergone both
25 an electrocardiogram and echocardiogram, and I am informed that the results of both the
26 electrocardiogram and echocardiogram were normal.
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