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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 WALTER F.
8) STEWART, PH.D, M.P.H. IN
9) SUPPORT OF OPPOSITION OF AHP
10) TO MOTION FOR CLASS
11) CERTIFICATION AND
12) PREFERENTIAL TRIAL SETTING
13)
14)
15) DATE: AUGUST 13, 1999
16) TIME: 10:00 A.M.
17) DEPT.: SE-D
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1 this action contend that all patients who took fenfluramine or dexfenfluramine, alone or in
2 combination with phentermine, for a period of one month or longer should have "medical
3 monitoring" for purposes of determining whether or not they suffer from valvular abnormalities or
4 primary pulmonary hypertension. I also understand that plaintiffs propose that all such patients,
5 regardless of individual circumstances, should receive monitoring, including an echocardiogram, for
6 the remainder of their lives.

7 8 **Summary of Opinion**

9 6. I have reviewed the available data concerning the possible relationship between
10 valvular heart disease and primary pulmonary hypertension and the ingestion of fenfluramine and
11 dexfenfluramine. Those data (including the data upon which plaintiffs rely) do not support the
12 proposition advanced by plaintiffs that everyone who ingested those drugs for one month or longer
13 is at an increased risk of contracting valvular heart disease or primary pulmonary hypertension
14 regardless of what drugs or combination of drugs were taken, at what doses, in what regimens, and
15 for what periods of time.

16 7. The data I have reviewed concerning fenfluramine and dexfenfluramine and their
17 possible relationship with valvular heart disease suggest that patients who took the drugs for three
18 months or less do not have an increased risk for developing abnormalities of the heart valves. In
19 addition to duration, drug dose and regimen, as well as other individual factors, could also influence
20 the risk of heart valve abnormalities.

21 8. The available data do not provide a basis for concluding that there is an excess risk
22 of cardiac valve abnormalities that emerges years after an individual stopped taking diet drugs. In
23 addition, the available data do not provide a basis for concluding that there is an excess risk of
24 progressive changes that emerges after an individual stopped taking diet drugs.

25 9. The data do not support plaintiffs' conclusion that there is an excess risk of PPH
26 among persons who took these drugs for three months or less; there is no statistically significant
27 difference in the rates of PPH for those who took diet drugs for three months or less and those who
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1 never used them at all. Furthermore, there is evidence that the risk of primary pulmonary
2 hypertension declines after the drugs are discontinued.

3 **Limitations of Epidemiological Studies**

4 10. Most epidemiological studies are observational in nature rather than experimental.
5 In other words, most epidemiological studies do not involve artificial manipulation of study
6 variables. As a result, epidemiological studies are often subject to certain types of errors and
7 limitations. Many of these errors may result in incorrect identification of an association or its cause.
8 Two important types of error that are common in epidemiological studies are bias and confounding.

9 11. Bias refers to a systematic variation in the study that results in study groups being
10 treated or evaluated differently. This systematic variation could be the true explanation of an
11 observed association. Thus, if bias is present, the study could appear to show an association when no
12 association actually exists. Bias does not mean that the observer intentionally skewed the results –
13 the observations could be accurate and truthful but still be biased.

14 12. There are many different types of bias. One is selection bias. Selection bias refers to
15 a distortion in the estimate of the association between exposure and disease that results from the
16 manner in which subjects are selected for the study population. Some causes of selection bias
17 include flaws in the study design (e.g., the choice of groups to be compared and choice of sampling
18 frame), loss to follow-up or non-response during data collection, and selective survival.

19 13. Another type of bias is information bias. Information bias refers to a distortion in the
20 estimate of effect that is due to measurement error or misclassification of subjects on one or more
21 variables. Sources of information bias include invalid or inconsistent measurement, incorrect
22 diagnostic criteria, and omissions, imprecisions, or other inadequacies in previously recorded data.
23 Because of possible information bias, results from different studies that use different measurement
24 techniques, or different equipment, or different test interpreters may not be comparable, particularly
25 if the measurement technique or interpretation is at all subjective. Information bias can also occur if
26 observers or subjects are not blinded to the exposure status of the study participants.

1 14. A bias in a study may be difficult, if not impossible, to correct at the analysis phase.
2 It is an error inherent in the study design. A statistically significant result does not mean that the
3 study is protected from bias or that the bias is unimportant.

4 15. The second major type of error is confounding. Confounding occurs when the effect
5 of the factor being studied (e.g., the effect of a drug) is mixed in the data with the effect of other
6 variables (e.g., the effect of obesity or hypertension). The confounding variable is related
7 independently to both the risk factor and the outcome variable, which could cause the data to appear
8 as if the risk factor and outcome variable are associated when they actually are not (or are not related
9 as strongly as the data would appear to suggest). Confounding, unlike bias, may be correctable by
10 various analytic techniques if it is not controlled by the study design.

11 16. There are many different types of study designs, with varying advantages and
12 disadvantages.

13 17. A case report is not a study, but a report of a single patient, sometimes one who was
14 exposed to a drug and experienced an adverse outcome. Case reports are useful for generating
15 hypotheses that can be tested in more formal studies, but otherwise are quite limited. The patient
16 cannot be assumed to be either typical of people who have taken the drug or typical of people with
17 the disease. Causation cannot be inferred from a single case report of an illness that has arisen in a
18 patient who has used a particular drug. It is impossible to tell whether the disease or adverse
19 outcome would have occurred in any case, even if the drug had not been taken. Case reports cannot
20 be used to quantify any possible risk or to determine who in a population may be at risk. For these
21 reasons, spontaneous reports of adverse events may be useful to generate hypotheses for further
22 testing, but should not be overinterpreted.

23 18. For example, an observation that a given event has occurred in a patient who has
24 taken a given drug for a period of time (e.g., one month) does not necessarily mean that anyone who
25 took the drug for that period of time is at increased risk for the same event. First, the drug may not
26 have caused the event. Second, these types of events occur in people who did not take the drug.
27 Third, there may be unusual or unique factors that explain the event and that do not apply to other
28 circumstances. Again, individual case reports cannot be used to quantify risk or to determine who,

1 if anyone, in a population may be at altered risk or to make any statements or conclusion about
2 causal connections.

3 19. A case series is a collection of patients who generally have all been exposed to a
4 given drug and whose clinical outcomes are then evaluated. It is usually unknown whether the
5 patients observed are typical of the population exposed to the drug. Therefore, even if the
6 observations are otherwise valid and accurate, they cannot necessarily be generalized to all patients
7 who took the drug. There usually is no control group, or only historical controls. It is usually not
8 possible to tell whether the disease or adverse outcome occurred before or after taking the drug, or
9 would have occurred even if the drug had not been taken. These critical questions regarding risk
10 can begin to be assessed only by selecting an appropriate control group. A case series is useful for
11 speculation, for generating hypotheses, and for suggesting certain associations. It is not appropriate
12 to use a case series to infer a relation of cause and effect.

13 20. The “gold standard” study design is the randomized clinical trial. A randomized
14 clinical trial is a true experiment in which subjects are randomly assigned to one of a series of
15 treatment or non-treatment groups. The random assignment of subjects makes it likely that the
16 study groups will be comparable in terms of potential confounding factors (both known and
17 unknown) and therefore will differ only by treatment with the drug being studied.

18 21. With randomized clinical trials, it is also possible to avoid or minimize potential
19 bias. Bias as the result of subjects being influenced by knowledge of drug treatment can be
20 removed or minimized by using placebos and not informing subjects what treatment they are
21 receiving, a process known as “blinding.” Bias as the result of the observer being influenced by
22 knowledge of treatment can be reduced by not informing the observer what treatment the subjects
23 are receiving, which is another type of blinding. For example, to reduce potential observer bias, an
24 echocardiographer examining a subject for valvular heart disease in a blinded clinical trial will be
25 kept unaware of whether or not the subject has received diet drugs.

1 phentermine). There was no control group. These data cannot not be generalized to people who
2 took dexfenfluramine or other drug regimens, or to people who took fenfluramine and phentermine
3 for shorter durations, among others.

4 27. The Connolly Article reports a series of cases; it does not provide a means of
5 estimating whether there is an association between use of diet drugs and valvular heart disease,
6 much less the size of such an association. As a poorly defined case series, it can only be used to
7 speculate about a possible relationship between treatment with fenfluramine and phentermine and
8 the development of valvular heart disease. It is unknown how many cases of regurgitation might
9 have been expected in the people selected absent drug treatment. As the authors of the article
10 themselves acknowledge, "definitive statements about a true association of valvular disease with
11 fenfluramine-phentermine therapy cannot be made" on the basis of the article.

12 28. I have reviewed the FDA Survey of 291 patients who had taken fenfluramine in
13 combination with phentermine (271 patients) or dexfenfluramine with or without phentermine (20
14 patients). These data are insufficient to establish that fenfluramine or dexfenfluramine increases the
15 risk of valvular regurgitation or to establish the magnitude of any such risk. There are no
16 guarantees that the patients included are typical of patients who took those drugs, and the
17 prevalence figures should not be generalized to the population of all patients who ever took
18 fenfluramine in combination with phentermine, or dexfenfluramine.

19 29. The FDA Survey is subject to multiple types of bias and from it one cannot infer the
20 magnitude or existence of any increased risk.

21 30. More specifically, the FDA data are subject to selection bias. For example, Dr.
22 Richard Bowen contributed 122 patients to FDA's data, representing approximately 45% of the 271
23 patients who had taken fenfluramine and phentermine. FDA described these 122 patients as
24 "asymptomatic," but Dr. Bowen, in an interview published in the Wall Street Journal on
25 September 18, 1997, stated that a number of the patients he reported had received echocardiograms
26 specifically because he had observed heart murmurs in them. Patients selected for testing because
27 they have cardiac murmurs would obviously bias the results towards higher observed levels of
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1 regurgitation. Other types of selection bias, such as patient self-selection, could also influence the
2 FDA data.

3 31. An additional indication that the FDA data were subject to selection bias is provided
4 by another article published in the Wall Street Journal on October 31, 1997, entitled "Diet Drug
5 Mystery Grows as New Data Emerge" by R. Langreth and L. Johannes. The writers collected
6 echocardiographic data on nearly 750 diet drug patients at 21 other sites around the country and
7 reported an observed frequency of regurgitation of 8% (as compared to a frequency reported in the
8 FDA Survey of more than 30%). It is important to recognize that the Wall Street Journal data also
9 may not be representative of patients who took diet drugs. The observation that two similar surveys
10 could produce such widely disparate results, however, illustrates why they cannot be used to
11 establish whether the drugs increase the risk of valvular regurgitation, much less used to quantify
12 any increased risk.

13 32. In addition to selection bias, the FDA Survey is also potentially subject to
14 information bias. There is no indication that the echocardiographic observations compiled in the
15 FDA Survey were made consistently or accurately by a single reader or by a calibrated set of
16 readers, or that technical personnel had received the same training or otherwise conducted the tests
17 in a consistent manner. All of these factors could bias the results, particularly if echocardiography
18 involves any degree of subjectivity in the conducting and interpretation of tests. Moreover, even if
19 the tests had been consistently and validly performed and evaluated, they could not be assumed to
20 be comparable to the tests performed on the historical control group.

21 33. Importantly, the echocardiography technicians and interpreters for the FDA Survey
22 were not blinded as to whether the patients had taken diet drugs. In order to minimize the
23 possibility of bias, anyone involved with performing or interpreting the echocardiographs should
24 have been unaware of whether the patients had taken diet drugs. Because the FDA Survey did not
25 utilize such blinding, it is possible that the investigators' expectations could have affected their
26 perceptions and judgments, even if on an unconscious level, and resulted in an artificially high
27 number of observations of valvular disease. Conversely, expectations that valvular heart disease
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1 was not prevalent in a control population of young healthy individuals conceivably could result in
2 artificially low numbers of observations.

3 34. The historical control group cited in the FDA Survey also appears to be an
4 inappropriate yardstick against which to measure observations. In selecting a control population, it
5 is important to use a population as much like the exposed population as possible. The similarities
6 help to decrease (but do not necessarily eliminate) the possibilities of confounding bias being
7 present. The 291 patients in the FDA Survey were an average of 47-48 years old, had an average
8 weight of approximately 210 pounds (of those whose weight was reported), and were almost
9 exclusively women. The controls cited by FDA, however, were healthy (non-obese) adults of both
10 genders, and substantially younger (aged 23-35). The fact that these populations are so different
11 introduces a number of potentially confounding factors (e.g., age, gender, weight, and other health
12 status) that are not sufficiently accounted for by FDA. Moreover, because the echocardiography in
13 the “control” group was performed by different technicians and interpreters and at different times
14 on different equipment, there is no guarantee that the regurgitation measured in the historical
15 controls is comparable to the regurgitation reported in the 291 diet drug patients. FDA’s own
16 regulations and guidance on clinical studies make clear that historical controls usually have
17 significant limitations and are generally disfavored for making quantitative assessments.

18 35. Finally, it should be noted that the FDA Survey data were collected almost
19 exclusively from long term users (average use of 1-2 years) of fenfluramine in combination with
20 phentermine. Even if the Survey were otherwise valid, the results could be generalized only to
21 people who took the same drugs for the same period of time.

22 36. The Connolly Article and the FDA Survey should not be relied upon to establish a
23 relationship between fenfluramine or dexfenfluramine and heart valve abnormalities. Since then,
24 more formal studies have been completed. These more recent studies demonstrate that individual
25 factors, such as dose/duration of treatment and perhaps drug regimen, among others, are important
26 determinants in defining that relationship.

The More Recent Studies

1
2 37. For example, a study published by Weissman NJ, et al., *An Assessment of Heart-*
3 *Valve Abnormalities In Obese Patients Taking Dexfenfluramine, Sustained Release*
4 *Dexfenfluramine, or Placebo*, New Eng. J. Med. 1998;339:725, was a randomized, controlled,
5 double-blinded clinical trial of dexfenfluramine, a true experimental study design that can minimize
6 many types of potential bias. As I discussed earlier, this type of study design is the “gold standard.”
7 Because dexfenfluramine has been taken off the market and is not available for future clinical trials,
8 it does not appear that data from another study of this quality will become available. Thus, the data
9 from this study are likely to be some of the best data concerning dexfenfluramine and the risk of
10 valvular heart disease and will probably be unique.

11 38. The Weissman study involved over 1000 obese patients who were randomly
12 assigned to one of three treatment groups: placebo, treatment with commercially available
13 dexfenfluramine, and treatment with experimental sustained-release dexfenfluramine. Patients were
14 not informed whether they were receiving dexfenfluramine or placebo. The random assignment of
15 patients should have minimized the effects of potential confounding factors or selection bias.
16 Patients were treated for an average of 75-77 days and then examined by echocardiography within
17 an average of 34 days following the end of treatment to determine whether there were any
18 differences demonstrated either by valvular morphology or by evidence of predetermined levels of
19 regurgitation. Echocardiographers were not informed of which patients had been treated with
20 dexfenfluramine, and echocardiograms were interpreted by one central laboratory according to a
21 standard protocol. The central reading and reader blinding should have minimized any
22 measurement or information bias.

23 39. Defining a case of aortic regurgitation as regurgitation of mild or greater degree (the
24 same definition FDA used in its survey), the study found no appreciable differences between
25 treatment groups. Similarly, defining a case of mitral regurgitation as regurgitation of moderate or
26 greater degree (the same definition FDA used in its survey), the study found no significant
27 differences between treatment groups.
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1 40. A different study by Dr. Ravin Davidoff, et al., examined the effect of short-term
2 treatment with fenfluramine (as opposed to dexfenfluramine). In the Davidoff study,
3 echocardiography was performed on a blinded basis on women who had taken part in a randomized
4 controlled trial of fenfluramine some four to five years earlier. The participants had been randomly
5 assigned to receive either fenfluramine (276 subjects) or placebo (254 subjects) for about three
6 months as part of a smoking cessation trial. This study design of follow-up on study participants
7 who had been randomly assigned to treatment groups in a blinded clinical trial is one of the
8 strongest study designs, certainly less prone to bias and confounding than the study design used by
9 Khan, which I discuss later. No significant differences in the prevalence of aortic or mitral
10 regurgitation were seen between the two groups in this study. The results strongly suggest either
11 that short-term treatment with fenfluramine is not associated with the development of valvular
12 regurgitation or that once four to five years has elapsed after treatment has ended, any drug-related
13 abnormalities that were present earlier have disappeared.

14 41. These two studies are further supported by the results of a study that was presented at
15 the annual meeting of the American Heart Association in November 1998 by Dr. Julius Gardin. In
16 this relatively large study, echocardiography was performed on subjects recruited from 25 clinics
17 specializing in obesity. 934 subjects had taken either (a) fenfluramine in combination with
18 phentermine or (b) dexfenfluramine, for at least 30 days, and 539 control subjects had not taken any
19 diet drug for more than five years. Echocardiogram interpretations were made without knowledge
20 of the subjects' treatment status. Among patients in the first group, all had echocardiography
21 performed with 14 months of stopping the drugs(s). The use of dexfenfluramine or fenfluramine in
22 combination with phentermine for three months or less was not related to any increase in the risk of
23 aortic or mitral valvular regurgitation by the FDA case definition.

24 42. The initial results of the largest echocardiographic study of
25 phentermine/fenfluramine to date were presented by Dr. Thomas Ryan, et al. at the annual meeting
26 of the American College of Cardiology on March 9, 1999. This study involved 1163 subjects who
27 had taken fenfluramine in combination with phentermine for varying periods of time and 672
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1 control subjects who had not taken any diet drug for more than five years. Echocardiographic
2 evaluations were made without knowledge of the subjects' treatment status.

3 43. With respect to aortic regurgitation, patients who had taken fenfluramine in
4 combination with phentermine for six months or less had no increased prevalence of regurgitation.
5 In those patients who took the drugs for more than six months, there was a statistically significant
6 increase in predominantly mild aortic regurgitation. With respect to mitral regurgitation, patients
7 who had taken fenfluramine in combination with phentermine had no statistically significant
8 increase in regurgitation meeting FDA criteria. The authors also reported no significant differences
9 between treated subjects and control subjects with respect to tricuspid or pulmonic valve
10 regurgitation as well as with respect to valve leaflet thickening or restricted mobility. There was
11 also no difference in frequency of clinical heart disease between the treated and untreated subjects,
12 no difference in pulmonary artery pressures, and no reports of endocarditis in any of the subjects.

13 44. Like the Gardin study, the Ryan study excluded from the control group those people
14 who had used diet drugs within the prior five years. Dr. Farquhar, in a footnote to ¶ 21 of his
15 February 24, 1999 report, has raised the possibility that the prevalence of regurgitation observed in
16 such control groups could have been influenced by including subjects who had used diet drugs more
17 than five years before the study. A number of assumptions would have to be true for that
18 hypothesis to be correct. Among other assumptions, a significant number of people in the control
19 group would have to have been exposed to diet drugs previously. Additionally, those people
20 exposed would have to have taken the drugs for a long enough period of time (certainly greater than
21 3 months) to have had any increased risk of regurgitation. The available data do not support these
22 assumptions.

23 45. The Gardin and Ryan studies commenced in 1997 and continued through 1998.
24 Dexfenfluramine was not on the market until 1996 and control group subjects thus would not have
25 been exposed to that drug. Data from National Prescription Data Plus providing the numbers of
26 prescriptions for Pondimin indicate that fenfluramine was not widely prescribed prior to the mid-
27 1990s and, according to the study criteria, people who used the drug in that time period would have
28 been excluded from the studies. Other data demonstrate that most people who used fenfluramine

1 used the drug for three months or less, a duration that is not associated with any increased risk of
2 valvular regurgitation. In light of these data, it is unlikely that the prevalence of regurgitation
3 observed in the control groups of the Gardin and Ryan studies was influenced to any significant
4 degree by the possibility of prior diet drug use. The low prevalence of regurgitation observed in the
5 control group of the Khan study is more likely a function of that particular study, including the
6 methodology used to select its control group (which was different from that used for the treatment
7 group) and imperfect blinding.

8 46. These four studies (Weissman, Davidoff, Gardin and Ryan) strongly suggest that
9 patients who used dexfenfluramine or fenfluramine for periods of three months or less are not at
10 increased risk of developing valvular heart disease. In fact, in the Ryan study, subjects who took
11 the drugs for up to six months had no increased risk of regurgitation.

12 47. With respect to longer term use of the drugs, Khan et al. performed echocardiograms
13 on 233 patients who previously had taken one or more diet drugs (dexfenfluramine alone,
14 dexfenfluramine in combination with phentermine, or fenfluramine in combination with
15 phentermine), and on 233 controls matched to the patients on weight and demographic
16 characteristics. Khan MA, et al., *The Prevalence of Cardiac Valvular Insufficiency Assessed By*
17 *Transthoracic Echocardiography In Obese Patients Treated With Appetite-Suppressant Drugs*,
18 *New Eng. J. Med.* 1998;339:713 ("Khan Study"). Although plaintiffs' expert Dr. John Farquhar
19 describes this study as a "case-control" study, it is, in fact, a cohort study and not a case-control
20 study. Patients on dexfenfluramine had used the drug for an average of approximately five months,
21 while patients on dexfenfluramine and phentermine had used the drugs for an average of nine
22 months, and patients on fenfluramine and phentermine had used the drugs for an average of more
23 than two years. Unlike the Weissman and other studies discussed above, echocardiogram readings
24 in this study were not uniformly performed on a blinded basis, nor were there standard definitions
25 used to define degrees of regurgitation. Also, because the control population did not come from the
26 same clinic as the patients who had taken diet drugs (instead, the control population responded to a
27 newspaper advertisement), the study results are potentially confounded. Because of methodological
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1 weaknesses in this study, especially in comparison to other more rigorous studies, the results of this
2 study should be interpreted cautiously.

3 48. Regurgitation was observed more commonly in users of diet drugs than in the
4 comparison subjects, although there appeared to be differences between groups of users. For
5 example, the prevalence of aortic regurgitation among patients who took dexfenfluramine alone
6 appeared to be approximately half of the prevalence reported among users of fenfluramine and
7 phentermine. It is not clear whether such differences are due to differences in duration of use, to
8 differences in the particular drug regimens, to both in combination, or to some other factor or
9 factors. The Khan study does not address the impact of recency of drug use on the prevalence of
10 valvular regurgitation, nor does it provide data on drug use for periods of three months or less. The
11 prevalence of observed regurgitation in the group that used fenfluramine in combination with
12 phentermine (which used the drugs for an average of approximately 27 months) cannot necessarily
13 be generalized to those who took the drugs for shorter periods of time. In fact, none of the results
14 from any of the groups should be generalized to those who took the drugs for shorter periods of
15 time than those studied.

16 49. In the Gardin study discussed earlier, aortic regurgitation in longer term users of
17 dexfenfluramine and users of fenfluramine in combination with phentermine was more common
18 than in patients who had not taken these drugs. The majority of this regurgitation was mild. Mitral
19 regurgitation meeting the FDA case definition was present in approximately the same percentage of
20 subjects whether or not they had taken a diet drug and regardless of how long the drug had been
21 taken; there was no increase in diet drug users.

22 50. All of the studies discussed so far have addressed the relationship between diet drugs
23 and valvular regurgitation detected by echocardiography. A cohort study by Jick, et al. provides
24 some data regarding valvular regurgitation detected in a different manner. Jick HA, et al., *A*
25 *Population Based Study of Appetite-Suppressant Drugs and the Risk of Cardiac-Valve*
26 *Regurgitation*, New Eng. J. Med. 1998;339:719 ("Jick Study"). Using data from the General
27 Practice Research Database in the U.K., Jick identified approximately 9000 users of diet drugs in
28 1988 or later. The incidence of otherwise unexplained clinically diagnosed regurgitation in these

1 persons (and in a matched group of obese persons who had not taken diet drugs) was determined
2 through July 1996. Among users of fenfluramine or dexfenfluramine, the rate of regurgitation was
3 related to the duration of use, with a higher incidence among patients who used the drugs for four
4 months or greater, compared to patients who used the drugs for one to three months or not at all.
5 Both figures were quite low, however. During the entire period of the study, only 11 of the diet
6 drug users (out of approximately 9,000) developed otherwise unexplained regurgitation.

7 51. In his Supplemental Declaration dated April 15, 1999, Dr. Farquhar argues that the
8 article by Singh JP, et al., *Prevalence and Clinical Determinants of Mitral, Tricuspid, and Aortic*
9 *Regurgitation (The Framington Heart Study)*, Am. J. Cardio. 1999;83:897-902 (“FHS”), supports
10 the conclusion that exposure to diet drugs causes valvular heart disease. However, the FHS is of
11 limited relevance for evaluating risk in the published studies exploring the possible relationship
12 between valvular regurgitation and the ingestion of fenfluramine and dexfenfluramine.

13 52. As explained above, in selecting a control population, it is important to use a
14 population as much like the exposed population as possible. The similarities help to decrease (but
15 do not necessarily eliminate) the possibilities of confounding bias being present. For example, if
16 the echocardiographic examinations performed in a “control” group are performed by different
17 technicians and interpreters and at different times on different equipment compared to the
18 examinations of a treatment group in a study, there is no guarantee that the regurgitation measured
19 in the controls is comparable to the regurgitation reported in the treatment group. In this sense,
20 using a control population from one study for comparison with a treated population in another study
21 is essentially the same as using an historical control. FDA’s own regulations and guidance on
22 clinical studies make clear that historical controls usually have significant limitations and are
23 generally disfavored for making quantitative assessments. Because the data from the FHS were
24 collected during different times (in some cases, up to seven years prior to some of the diet drug
25 studies) on different equipment by different technicians and interpreted by different physicians
26 compared to the diet drug studies, they should not be used to make the sort of quantitative
27 assessments contained in Dr. Farquhar’s Supplemental Declaration. The FHS methodology should
28 not be assumed to be comparable to the methodologies of other studies. The only way to ensure

1 comparability between control groups and treatment groups is to obtain and read the
2 echocardiograms in a blinded fashion in the same study.

3 53. Additionally, a control group ideally should be selected from the same population as
4 those who were treated with diet drugs. Randomization of study subjects to treatment and non-
5 treatment groups, such as was performed in the Weissman and Davidoff studies, is the best method
6 of accomplishing this goal. For studies of cohorts of patients who were clinically treated with diet
7 drugs because they sought medical care for weight loss, another method of pursuing this goal would
8 be to use a control group that also sought medical care for weight loss, such as was performed in the
9 Gardin study (but not in the Khan study). Rates of regurgitation in a more general population, such
10 as in the FHS, should not be assumed to be appropriate controls for a population seeking care for
11 weight loss and treated with diet drugs.

12 54. It is not surprising, therefore, that the prevalence rates of regurgitation in the Khan
13 study control group are similar to those in the FHS. The control group in the Khan study was not
14 selected from the same population as the treatment groups in that study, and is more likely to be
15 similar to the population of the FHS.

16 55. Dr. Farquhar's use throughout his Supplemental Declaration of the FHS
17 regurgitation rates in 40-49 year old women as representative of background regurgitation rates in
18 control patients not exposed to diet drugs is inappropriate for a number of reasons. As Dr. Farquhar
19 himself states in ¶ 19, "age exerts a profound influence on the prevalence of valve regurgitation."
20 In the FHS, the prevalence of mild or greater aortic regurgitation in women aged 60-69, for
21 example, was nearly 10 times the prevalence of such regurgitation in women aged 40-49. A
22 population of women that has an average age of 48 is not the same thing as a population consisting
23 solely of 48 year old women. Using regurgitation rates from a single age category to generalize to a
24 population with more diverse ages is scientifically inappropriate unless the prevalence of
25 regurgitation increases with age in a linear fashion. The FHS data indicate that the prevalence of
26 regurgitation does not increase in a linear fashion. Gender is also relevant, as the FHS indicates that
27 men and women have different rates of aortic regurgitation. It therefore is incorrect to generalize
28 rates for only women to control group patients who included some men.

1 that there is an excess risk of progressive changes that emerges after an individual stopped taking
2 diet drugs.

3 59. As explained above, case reports cannot be used to quantify any possible risk or to
4 determine who in a population may be at risk. The individual events cannot be assumed to be
5 associated with or caused by the exposure. Case reports of patients who were observed to have
6 regurgitation following exposure to diet drugs for one to two months do not establish the
7 proposition that such short term exposure can result in regurgitation. This principle applies whether
8 a case report is reported individually or whether it is plucked out of a larger epidemiologic study. In
9 particular, selecting cases from a large study that meet some after the fact subjective criteria is
10 unscientific and offers no meaningful information about risk.

11 60. Dr. Farquhar's assertion in ¶ 33 of his February 24, 1999 report that the Weissman
12 study supports the conclusion that diet drug use of one month can result in regurgitation is incorrect
13 for a number of reasons. First, such a conclusion is nothing more than speculation. The Weissman
14 study does not provide data on the distribution of regurgitation according to duration of treatment –
15 it is not possible to determine from the data provided whether any cases of regurgitation at all
16 occurred among subjects who used the drugs for one month or who used the drugs for two months,
17 much less whether there was any significant increase in regurgitation compared to controls. Any
18 attempt to estimate an increased risk for regurgitation at one month's duration of diet drug use
19 without the underlying individual data is inherently unreliable and unverifiable.

20 61. Second, Dr. Weissman, et al., have presented follow-up data on their patient
21 population at the recent annual meeting of the American Society of Echocardiography.
22 Weissman NJ, et al., Does The Increased Prevalence Of Regurgitation Association With Appetite
23 Suppressants Persist 3-5 Months After Discontinuation Of Medication?, J. Am. Soc'y Echo.
24 1999;12 (Abstract 7A) ("Weissman II"). The investigators performed an additional
25 echocardiographic examination on 941 of the initial 1072 patients three to five months after they
26 discontinued medication (the initial echocardiograms were performed approximately one month
27 following discontinuation of the drugs). They reported that there were no significant differences in
28 the prevalence of aortic or mitral regurgitation between groups, whether measured by FDA criteria

1 or by any degree of regurgitation. They also reported that there were no differences in the
2 prevalence of restricted posterior mitral leaflet mobility. Weissman II confirms that there is no
3 increased risk of valvular regurgitation in patients who took dexfenfluramine for three months or
4 less.

5 62. Dr. Farquhar's assertion in ¶ 35 of his February 24, 1999 report that the Gardin study
6 showed an increased prevalence of regurgitation in groups exposed for three months or less is
7 simply factually incorrect. Even when compared by all grades of regurgitation (not just
8 regurgitation meeting the standard FDA case definition), there was no increase in aortic
9 regurgitation for either the dexfenfluramine group or the phentermine/fenfluramine group treated
10 for three months or less. In fact, there were NO cases of mild, moderate, or severe aortic
11 regurgitation among the group treated with dexfenfluramine for three months or less, compared
12 with approximately 4% of the control group. By Dr. Farquhar's reasoning, such data support
13 a conclusion that short-term dexfenfluramine protects against aortic regurgitation. Avoiding jumps
14 to such unsupported conclusions is precisely why epidemiologists employ tests of statistical
15 significance. With respect to mitral regurgitation, although phentermine/fenfluramine was
16 associated with a small increase in mild mitral regurgitation when compared by all grades of
17 regurgitation, dexfenfluramine for three months or less was not associated with any increase in
18 mitral regurgitation. The Gardin study does not provide data on the distribution of regurgitation
19 within the group of subjects who took drugs for three months or less, and any hypothesis that
20 regurgitation was increased in subjects who took the drugs for one month or more is pure
21 speculation that is not even consistent with the data.

22 63. The Davidoff, et al. study also does not support any hypothesis that use of diet drugs
23 for a period of time less than three months can cause regurgitation. Davidoff found no statistically
24 significant increases in risk of aortic or mitral regurgitation, whether measured by FDA criteria or
25 by any degree of regurgitation, in patients who had taken short-term fenfluramine. That study also,
26 in fact, found no significant differences in aortic or mitral leaflet thickening or mobility.

1 over time, from 17.4% before exposure to diet drugs to 15.2% following exposure. Second, there
2 were only two patients who had development of regurgitation meeting FDA criteria and both had
3 questionable associations with diet drugs. The first of the two patients had preexisting regurgitation
4 associated with a bicuspid aortic valve, which the authors stated may also have been responsible for
5 the progression of regurgitation. That patient's physicians had also read her serial echocardiograms
6 clinically as not in fact showing any progression of regurgitation. The second patient's baseline
7 echocardiogram was more than eight years prior to taking diet drugs, a long time period that the
8 authors acknowledged made any conclusion about progression less certain. In contrast, there were
9 two patients who had regurgitation at baseline that met FDA criteria and then regressed after taking
10 diet drugs. Third, the authors reported no statistically significant differences in the rates of
11 regurgitation observed over time. These data do not indicate that diet drugs cause progression of
12 valvular regurgitation.

13 69. As Dr. Farquhar points out in ¶¶ 44-46 of his February 24, 1999 report, there is an
14 increasing prevalence of regurgitation with increasing age, and there are other risk factors for
15 regurgitation, such as hypertension, that are present in the population that has taken diet drugs.
16 Thus, if one were to observe a population of non-diet drug users over time, one would expect to see
17 an increase in prevalence of regurgitation due simply to the effects of aging and other processes.
18 These same increases in regurgitation over time, unassociated with diet drugs, would be expected in
19 the population that has taken diet drugs. Such increases in regurgitation cannot be said to be caused
20 by diet drugs.

21 70. Dr. Farquhar does not cite in his report any epidemiological study demonstrating that
22 any observed regurgitation in diet drug patients progresses over time. I am unaware of any such
23 study. In fact, the few epidemiological studies that provide relevant data show no progression or
24 suggest some regression. Based on the available data, it is not possible to conclude to a reasonable
25 degree of scientific certainty that any regurgitation associated with diet drugs progresses over time.
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**There Is No Known Biologic Mechanism For
Valvular Regurgitation Associated With Diet Drugs**

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71. There is no generally accepted biologic mechanism by which diet drugs may cause valvular regurgitation. Although some people have hypothesized a mechanism involving serotonin, that hypothesis seems unlikely based on data indicating that fenfluramine does not, in fact, increase serum serotonin. For example, Redmon, et al. reported that patients taking fenfluramine and phentermine for an average of 11 months had either normal or reduced serum serotonin levels. Redmon B, et al., Letter to the Editor, New Eng. J. Med. 1997;337:1773-1774. Administration of fenfluramine has been reported to reduce blood levels of serotonin in a patient with carcinoid syndrome. Stahl SM & Levin B, Letter to the Editor, New Eng. J. Med. 1982;306:429. Finally, use of fenfluramine in children with autism also was reported to reduce blood serotonin levels. Geller E, et al., *Preliminary Observations on the Effect of Fenfluramine on Blood Serotonin and Symptoms in Three Autistic Boys*, New Eng. J. Med., 1982;307:165-169.

FDA Case Definition

72. Dr. Farquhar criticizes the use of the FDA case definition for valvular regurgitation in ¶¶ 16-18 of his February 24, 1999 report. Use of the FDA criteria in epidemiologic studies is not only appropriate but preferable in many respects to other criteria. As Dr. Farquhar points out, FDA adopted its case definition of valvular regurgitation in order to minimize misclassification and avoid confusion with background regurgitation of milder levels. Given the subjectivity and variability inherent in echocardiographic evaluations, setting a predefined threshold level of regurgitation that is the subject of interest in an epidemiologic echocardiographic study is good practice. The FDA criteria have also become widely accepted as the standard measurement of regurgitation of interest, which helps the scientific community communicate effectively and consistently about different study results. Although the FDA criteria do not purport to define regurgitation that is clinically meaningful, they are sufficiently broad that they would capture regurgitation that is clinically meaningful. In light of all of these factors, use of the FDA criteria in epidemiologic studies provides an appropriate and meaningful standard.

Primary Pulmonary Hypertension

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2 73. An association has been observed between the use of diet drugs (including, but not
3 limited to, fenfluramine and dexfenfluramine) and the incidence of primary pulmonary hypertension
4 (PPH). Abenheim L., et al., *Appetite-Suppressant Drugs and the Risk of Primary Pulmonary*
5 *Hypertension*, New Eng. J. Med. 1996;335:609. However, even if this association were to be a
6 causal one, the data do not support plaintiffs' conclusion that there is an excess of risk of PPH
7 among persons who took these drugs for three months or less; there is no statistically significant
8 difference in the rates of PPH for those who took diet drugs for three months or less and those who
9 never used them at all. Furthermore, there is evidence that with increasing time since a person's last
10 use of diet drugs, the risk of PPH declines. Because PPH is such a rare disease (approximately 1-2
11 per million per year), the absolute risk even in a long-term user of diet drugs is quite small,
12 especially one year or more after the drug has been discontinued. Whether a diet drug user is at
13 increased risk, if any, for PPH thus depends not only on dose/duration of treatment, but also how
14 long it has been since the patient last took the drugs, and probably other individual factors.

Screening Programs

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17 74. Although there may be an intuitive appeal that screening for a given disease or
18 condition will lead to earlier and more effective treatment, this assumption is not true in all cases.
19 Whether or not a screening program is justified depends on a number of factors, including the
20 characteristics of the disease or condition, the characteristics of the screening test, the prevalence of
21 the disease or condition in the population to be tested, and costs and benefits, among other factors.
22 These factors vary from test to test and from medical condition to medical condition and must be
23 evaluated for each individual screening program under consideration.

24 75. For example, in order for screening to be effective, it must be true that treatment at a
25 preclinical stage (that is, before the patient becomes symptomatic), is more effective than treatment
26 given after symptoms develop. Unless such earlier intervention makes such a difference, then
27 screening is neither necessary nor effective. Screening for lung cancer by chest x-ray, for example,
28 has been shown not to be effective because the prognosis is equally poor regardless of when

1 treatment is instituted. The point is that earlier identification of a disease or condition should not be
2 assumed to lead to clinical treatment benefits. Rather, like the American Cancer Society
3 recommends with respect to possible screening tests for cancer, there must be good evidence that
4 each test or procedure recommended is medically effective in reducing morbidity or mortality.

5 76. The screening test itself should ideally be reliable, valid, reproducible, inexpensive,
6 and easy to administer. Tests that have high levels of intraobserver or interobserver variability, or
7 that use vague or subjective criteria, are generally not very useful as screening tests.

8 77. The disease or condition to be screened for generally should appear in the target
9 population in a high prevalence in order to justify the costs of screening. This principle is reflected,
10 for example, in guidelines restricting mammography in younger women to those who have a family
11 history of breast cancer.

12 78. In evaluating the costs and benefits of a screening program, it is important to identify
13 the physical risks and economic costs of follow-up diagnostic procedures, particularly for those who
14 may be falsely identified as having the condition or disease. Early testing may result in false
15 positives that lead to unnecessary and possibly hazardous diagnostic procedures.

16 79. Any benefits of any knowledge gained concerning the health of former users of diet
17 drugs in aggregate who were monitored primarily would accrue not to the monitored populations
18 (i.e., the class members), but rather to any potential future users of these drugs. In this case,
19 however, any knowledge will have limited applicability in the future because the drugs have been
20 removed from the market. Moreover, the benefits, if any, would not bear on the public's health in
21 any additional way. (In contrast, if the condition being screened for were a communicable disease,
22 the public at large would have an interest in screening for the condition). Furthermore, even if one
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1 wished to monitor the health status of former users of diet drugs for research purposes, there are
2 more cost-effective ways of doing this than periodic examinations and diagnostic tests.

3 I declare under penalty of perjury under the laws of the State of California that the foregoing
4 is true and correct.

5 Executed this ____ day of July, 1999 at Baltimore, Maryland.

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7 _____
8 WALTER F. STEWART, PH.D., MPH
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