Adverse Event Reports from Metabolife

Prepared for
Sen. Richard J. Durbin
Rep. Henry A. Waxman
Rep. Susan A. Davis

Minority Staff Report
Special Investigations Division
Committee on Government Reform
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EXECUTIVE SUMMARY

The largest manufacturer of dietary supplements containing ephedra is Metabolife International, Inc. Prior to August 2002, Metabolife repeatedly informed the Food and Drug Administration that the company had "never been made aware of any adverse health events by consumers of its products." It also consistently maintained that its products are "absolutely safe."

In August 2002, press accounts revealed that the Justice Department was investigating the truthfulness of Metabolife's statements that the company had never received any adverse health reports. Shortly thereafter, Metabolife gave FDA copies of over 13,000 reports the company had received between 1997 and 2002 of adverse reactions to it products. Metabolife also gave copies of these records to Sen. Richard J. Durbin and Reps. Henry A. Waxman and Susan A. Davis.

This report is the first independent analysis to examine the adverse event reports produced by Metabolife. It finds that the reports involve many significant adverse events and conflict with Metabolife's statements that it was unaware of consumer reports of adverse health effects. Moreover, the report finds that Metabolife took a careless approach to the adverse event reports, did not report them in a timely fashion to FDA, and routinely failed to obtain the medical records necessary to evaluate the safety of its products.

Key Findings

The Metabolife records include nearly 2,000 reports of significant adverse reactions to Metabolife products. The adverse events reported to Metabolife by consumers of its products include 3 deaths, 20 heart attacks, 24 strokes, 40 seizures, 465 episodes of chest pains, and 966 reports of heart rhythm disturbances. In addition, the reports contain hundreds of consumer complaints of high blood pressure and disturbing psychiatric symptoms, such as anxiety, mood changes, or psychosis. In at least 46 instances, consumers reported that they required hospitalization following use of Metabolife products, and in at least 82 additional instances, consumers reported that they required emergency room care. In numerous adverse event reports, consumers told Metabolife that their doctors had indicated that Metabolife's products had caused the adverse health effects.

The Metabolife records indicate that many of the significant adverse events involve consumers who were young, in good health, and taking recommended dosages. Metabolife has asserted that adverse events do not occur when healthy individuals follow Metabolife's recommended dosages. The actual adverse event reports, however, include many reports of significant health effects in healthy consumers taking recommended dosages. Among the most significant adverse event reports (those involving heart attacks, seizures, strokes, and psychosis), over 90% of the reports where dosage information is noted involve consumers who were taking the dosage recommended by Metabolife. Among the significant adverse event reports where age

is noted, over 50% of the reports involve consumers under the age of 35. In hundreds of cases of significant adverse events, the consumers involved reported that they had no prior medical problems.

Metabolife's handling of the adverse event reports exhibits indifference to the health of consumers. Nearly 90% of the reports of significant adverse events submitted by Metabolife omit basic information, such as the age or gender of the consumer, or the date of the report. Nearly one-third of the reports of significant adverse event reports are handwritten, with notes that are sometimes illegible. In over 98% of the significant adverse event reports, there is no mention of Metabolife requesting the additional medical records needed for Metabolife to evaluate the role of its products in the adverse events. FDA regulations require drug manufacturers to report adverse events involving hospitalization, a life-threatening adverse reaction, or death within 15 days of receipt. In no instance did Metabolife report adverse events involving hospitalization, life-threatening adverse reactions, or death to FDA prior to its August 2002 submission.

The Metabolife records contradict Metabolife's claims that it was unaware of consumer complaints of adverse health effects. On repeated occasions, Metabolife told federal regulators that it had never received reports of adverse health effects from its consumers. In February 1999, for example, Metabolife informed FDA: "Metabolife has never been made aware of any adverse health events by consumers of its products. Metabolife has never received a notice from a consumer that any serious adverse health event has occurred." Metabolife, however, had received at least 138 reports of significant adverse events before these statements were made, including reports of heart attacks, strokes, seizures, and psychosis.

I. BACKGROUND

While ephedra-containing herbs in the form of teas have been used in Chinese medicine for centuries, the last decade has seen a steep rise in consumption of ephedra-containing dietary supplements.[1] Medical experts have raised questions about the safety of these supplements, which typically combine a concentrated dose of ephedra with another stimulant, such as caffeine, and are marketed for long-term use. Articles published in the medical literature have implicated the products in cases of heart arrhythmia, heart attack, stroke, seizure, psychosis, mood disorders, and death.[2]

The largest U.S. manufacturer of ephedra-containing dietary supplements, Metabolife International, Inc., has disputed these concerns. Metabolife, according to its website, is one of the fastest growing companies in the United States, and "is the top retailer of weight management products in the U.S."[3] Metabolife's revenue exceeded one billion dollars in 1999.[4] Its principal product is an ephedra-caffeine supplement called Metabolife 356.

As concerns about ephedra-containing supplements have grown, Metabolife has consistently maintained that its products are safe. In 1999, in an interview with ABC's 20/20, then-company president Michael Ellis said: "our product is absolutely safe."[5] In 2001, Garry Pay, General Counsel of Metabolife, wrote: "The use of ephedrine-containing supplements (with

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[1] *U.S. in Criminal Inquiry on Metabolife Product*, New York Times (Aug. 16, 2002).

[2] See, e.g., Christine A. Haller and Neal L. Benowitz, *Adverse Cardiovascular and Central Nervous System Effects Associated with Dietary Supplements Containing Ephedra Alkaloids*, New England Journal of Medicine, 1833-8 (Dec. 21, 2000); D. Samenuk, M. Link, M. Homoud, et al., *Adverse Cardiovascular Events Temporally Associated with Ma Huang, an Herbal Source of Ephedrine*, Mayo Clinic Proceedings, 12-16 (January 2002); H. Doyle and M. Kargin, *Herbal Stimulant Containing Ephedrine Has Also Caused Psychosis*, British Medical Journal, 756 (Sept. 21, 1996); J. Bailes, R. Cantu, A. Day, *The Neurosurgeon in Sport: Awareness of the Risks of Heatstroke and Dietary Supplements*, Neurosurgery, 283-288 (August 2002); K. Zahn, R. Li, R. Purssell, *Cardiovascular Toxicity After Ingestion of "Herbal Ecstasy,"* Journal of Emergency Medicine, 289-291 (March-April 1999); A. Bruno, K. Nolte and J. Chapin, *Stroke Associated With Ephedrine Use*, Neurology, 1313-1316 (July 1993); R. Capwell, *Ephedrine-Induced Mania from an Herbal Diet Supplement*, American Journal of Psychiatry, 647 (April 1995).

[3] *About Metabolife* (on line at www.metabolife.com/about/history.htm).

[4] *Metabolife Inquiry Renews Focus on Safety*, Los Angeles Times (Aug. 17, 2002).

[5] *Findings from Investigation of Metabolife*, 20/20, ABC (Oct. 15, 1999).

or without caffeine) has been studied and repeatedly found to be safe and effective in several clinical trials."[6]

Metabolife has also repeatedly asserted to federal regulators that it had received no reports of adverse health effects from its consumers. In April 1998, Metabolife's then-president, Michael J. Ellis wrote to FDA: "Metabolife has never received one notice from a consumer that any serious adverse health event has occurred because of the ingestion of Metabolife 356."[7]

In February 1999, the company's chief counsel wrote FDA:

> Metabolife has never been made aware of any adverse health events by consumers of its products. Metabolife has never received a notice from a consumer that any serious adverse health event has occurred because of ingestion of Metabolife 356 . . . . [Customers'] continued use of the product without reporting any serious adverse effects demonstrates the safety of the product. . . "[8]

On August 16, 2002, press reports revealed that the Justice Department was investigating the truthfulness of these statements to FDA.[9] Following these reports, Metabolife voluntarily turned over more than 13,000 redacted adverse event reports to FDA. At the same time, these reports were also provided to selected members of Congress, including Sen. Richard J. Durbin and Reps. Henry A. Waxman and Susan A. Davis.[10]

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[6]Letter from Garry T. Pay, General Counsel, Metabolife, to Paul Tagliabue, Commissioner, National Football League (Oct. 3, 2001) (on line at www.metabolife.com/about/nfl.htm). This letter was written in response to the NFL's decision to ban ephedrine.

[7]Letter from Michael J. Ellis, President of Metabolife, to FDA Docket No. 98N-0148 (Apr. 17, 1998).

[8]Letter from Allen P. Beinke, Counsel for Metabolife, to FDA Docket No. 98N-0148 (Feb. 9, 1999).

[9]*Officials Open Criminal Probe on Metabolife*, Wall Street Journal (Aug. 16, 2002).

[10]Members of Congress had requested these reports since 1999. Letter from Rep. Henry A. Waxman to Mr. Michael J. Ellis, CEO, Metabolife International, Inc. (Aug. 16, 1999). As recently as July 17, 2002, Senator Durbin asked in a letter that Metabolife "share with me the total number of adverse events relating to your dietary supplement products, received by your company since the enactment of the Dietary Supplement Health and Education Act of 1994." Letter from Senator Richard J. Durbin to Mr. David Brown, President and CEO of Metabolife International Inc. (July 17, 2002). Metabolife responded on July 30, 2002 by saying that the company was only aware of 78 "unproven, anecdotal allegations of, or references to," strokes, heart attacks, seizures and deaths. Letter from Mr. Lanny Davis, Counsel for Metabolife to Ms. Melanie Leitner, Congressional Fellow with Senator Richard J. Durbin (July 30, 2002).

This release of records was not accompanied by any change in Metabolife's position regarding the safety of its products. The company has since released three reviews of the adverse event reports, each paid for by Metabolife, and each concluding there is no evidence of danger from ephedra products.[11] According to the company, one reviewer found that "there is no demonstrable connection between use of Metabolife 356 and any of the conditions reported by the Health Line callers."[12] In a letter to Health and Human Services Secretary Thompson, David Brown, President of Metabolife wrote: "experts have reviewed these files and have concluded that they do not in any way demonstrate that ephedra is unsafe or poses any health problems. We . . . firmly stand behind the safety and efficacy of our product."[13] And Metabolife's president told the National Institutes of Health: "we are confident the product is safe for consumers."[14]

Information available on Metabolife's website minimizes the risk of any adverse reactions to consumers. According to Metabolife, adverse event reports "provide no evidence that ephedra-based supplements have caused any serious adverse events when used: (1) responsibly for weight control; (2) at recommended dosages; and (3) by those individuals who do not have certain medical conditions described on our labels."[15] In a recent letter to the public also posted on Metabolife's website, the company's president wrote: "any noticeable side effects are minor and fleeting in nature."[16]

II. PURPOSE AND METHODOLOGY

At the request of Sen. Durbin and Reps. Waxman and Davis, this report provides the first independent analysis of the adverse event reports submitted by Metabolife. The report was prepared by the Special Investigations Division of the minority staff of the Committee on Government Reform of the U.S. House of Representatives, in conjunction with the majority staff

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[11]Steven B. Karch, M.D., *An Analysis of Metabolife 356 HealthLine Contacts* (Aug. 15, 2002); Craig A. Molgaard, *"Epidemiologic Assessment of Health Line Reports About a Dietary Supplment* (Aug. 2002); Ashraf Mozayani, PharmD., Ph.D., D-ABFT, *Analysis of Metabolife 356 Health Line Reports* (Aug. 2002).

[12]*Summary of Expert Opinions: Metabolife's Healthline Reports* (on line at www.metabolife.com/about/healthlinesummary.htm).

[13]Letter from David Brown, President of Metabolife, to Secretary Thompson (Aug. 15, 2002).

[14]Letter from David Brown, President of Metabolife, to Paul M. Coates, Ph.D., Director, Office of Dietary Supplements, National Institutes of Health (Aug. 21, 2002).

[15]Letter from Garry T. Pay, General Counsel, Metabolife, to Paul Tagliabue, Commissioner, National Football League (Oct. 3, 2001) (on line at www.metabolife.com/about/nfl.htm).

[16]*From Our Vantage Point -- A Letter from David Brown, President of Metabolife* (on line at www.metabolife.com/about/justthefacts.htm).

of the Subcommittee on Oversight of Government Management, Restructuring and the District of Columbia of the Governmental Affairs Committee of the U.S. Senate.

The report is based on an analysis of the more than 13,000 adverse event reports that were provided by Metabolife. These reports, which cover the period from 1997 to the present, consist of the notes taken by Metabolife representatives handling phone calls from consumers reporting adverse health effects. The notes were redacted by Metabolife to remove identifying information.

The reports were provided to Sen. Durbin and Reps. Waxman and Davis in 14,459 computer files on compact disc by Metabolife in August and September 2002. These files were in the form of numbered images without searchable fields. One adverse event report might stretch across several images; alternatively, as many as five adverse event reports might be found on a single image. Two additional reports were provided separately by Metabolife to Sen. Durbin's staff.

To facilitate analysis of the adverse event reports, the Special Investigations Division created a searchable database of the adverse event reports. The original Metabolife files were individually reviewed, and reports involving three categories of significant adverse events previously linked to ephedra use by medical experts were input into the database. These three categories of significant adverse events were: (1) cardiac symptoms and conditions, including heart attack, chest pain, arrhythmia or racing heart, and high blood pressure; (2) neurological symptoms, including stroke and seizures; and (3) psychiatric symptoms and complaints, including psychosis, anxiety, and mood changes.

As part of the analysis, the records were assessed for the following information: (1) whether the report involved an emergency department visit or hospitalization; (2) whether the consumer's doctor indicated that ephedra could be responsible for the medical problem; (3) whether the consumer was under age 35; (4) whether the consumer was overweight, as measured by body mass index (BMI); (5) whether there is any mention of the consumer's prior medical condition; and (6) in the case of events involving heart attack, stroke, seizure, and psychosis, whether the dosage taken by the consumer was noted.

The records were also assessed to evaluate the quality of Metabolife's recordkeeping and follow-up. Each record in the database was assessed for several indicators of quality of response, including whether the records were typed or handwritten, whether the records include basic information, specifically: (1) the date of the report; (2) the gender and age of the consumer; and (3) whether there was any indication that Metabolife had sought to obtain medical records. In addition, Metabolife's adverse event reports were compared with FDA standards for mandatory reporting of adverse events for drugs. These standards require that: (1) the manufacturer must submit to FDA an adverse event report within 15 days for any unexpected hospitalization, life

threatening event, serious medical condition, or death; (2) the report must contain specified information, including age, gender, and date of event and of report; and (3) the manufacturer must promptly investigate each such event and submit follow-up information.[17]

Several measures were taken to enhance the accuracy of this analysis. All reports involving the most significant adverse events – stroke, heart attack, seizure, and psychosis – were reviewed multiple times to ensure accuracy. In addition, any adverse event reports that appeared to be duplicates or were on a list supplied by Metabolife as duplicates of other reports were eliminated from the database. Finally, the list of reports for which Metabolife requested medical records was checked against a list of medical records submitted by Metabolife. For the purposes of the analysis, Metabolife was treated as having sought medical records if the company either documented a request for medical records or had some relevant medical records in its possession.

III. FINDINGS

A. The Metabolife Records Include Nearly 2,000 Reports of Significant Adverse Events

The reports submitted by Metabolife include 1,985 reports of significant adverse effects. The reports include:

- 3 reports involving deaths of consumers;[18]
- 1,667 reports involving cardiovascular problems or conditions, including 20 heart attacks, 465 episodes of chest pain, 966 rhythm disturbances, and 336 reports of high blood pressure;
- 64 reports involving neurological problems or conditions, including 24 strokes and 40 seizures; and
- 321 reports involving psychiatric symptoms, including 5 reports of psychosis, 230 reports of anxiety, and 95 reports of mood changes.[19]

Metabolife did not routinely ask consumers reporting adverse health effects about the type of medical attention they received. However, some of the adverse event reports did contain

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[17] 21 CFR 314.80(c)(1).

[18] One of these reports involved a 35-year-old woman who suffered a heart attack; another involved a 50-year-old woman with a possible arrhythmia; a third involved a woman with a cerebral hemorrhage.

[19] The totals do not add up to exactly 1,985 because some individual reports included more than one condition or disorder.

this information. In 33 reports of cardiac problems, 10 reports of neurological problems, and 3 reports of psychiatric problems, it was noted that consumers required hospitalization. In 82 additional reports, it was noted that the consumers required emergency room care.

Metabolife also did not routinely ask consumers whether their doctors had indicated that Metabolife products may have caused the adverse health effects. Nevertheless, such information was sometimes recorded in the adverse event reports. At least 51 consumers reporting cardiac problems, 11 reporting neurological conditions, and 3 reporting psychiatric problems told Metabolife that their physicians had indicated that ephedra may have caused their clinical condition.

B. Adverse Events Occurred in Previously Healthy People, in Young Consumers, and at Recommended Doses

In public statements, Metabolife has maintained that there is no evidence that adverse events have occurred in healthy individuals using its products at recommended dosages. For example, as quoted above, the company's website states that adverse event reports "provide no evidence that ephedra-based supplements have caused any serious adverse events when used: (1) responsibly for weight control; (2) at recommended dosages; and (3) by those individuals who do not have certain medical conditions described on our labels."[20]

The actual adverse event reports submitted by Metabolife, however, reveal that many of the significant adverse events involved consumers who followed recommended dosages, reported no prior medical conditions, and were young and not overweight.

To assess whether the adverse event reports were associated with taking excessive dosages of Metabolife's products, every adverse event report involving a heart attack, stroke, seizure, or psychosis was examined to determine if the report indicated the dosage taken by the consumer.[21] In 28 of the reports involving these conditions, dosage information is provided in the reports. In 27 of the 28 reports (96.4%), the dose was in the range recommended by the company.[22]

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[20]Letter from Garry T. Pay, General Counsel, Metabolife, to Paul Tagliabue, Commissioner, National Football League (Oct. 3, 2001) (on line at www.metabolife.com/about/nfl.htm).

[21]According to information on its website, Metabolife recommends that consumers take no more than eight tablets of Metabolife 356 per day. *Our Products* (on line at www.metabolife.com/products/356_detail.htm).

[22]The directions for use on Metabolife's website read: "Directions: As a dietary supplement, adults, 1 to 2 caplets 2 to 3 times a day, or every 4 hours, on an empty stomach 1 hour before meals. Do not exceed 8 caplets per day." *Our Products* (on line at www.metabolife.com/products/356_detail.htm).

Metabolife did not conduct any systematic assessment of medical history in the adverse event reports. In numerous reports, however, the consumers reporting the adverse health effects informed Metabolife that they had no prior medical conditions. The reports show that at least 332 consumers with cardiac problems, 10 with neurological problems, and 53 with psychiatric conditions affirmatively informed Metabolife that they did not have previous medical conditions. Moreover, at least 19% of the reports involving heart attack, stroke, seizure, or psychosis were filed by consumers who reported no prior medical problems.

Where age was noted, half of the cardiac reports (50.7%), more than one-third of the neurological reports (42.3%), and the psychiatric reports (53.0%) involved consumers under the age of 35.[23] Young Metabolife consumers also suffered over one-third (36.5%) of the heart attacks, seizures, strokes, and psychosis reported to the company where age was known.

The company's adverse event reports also indicate that many of the consumers reporting adverse health effects were not overweight. Among reports of significant cardiac, neurologic, and psychiatric problems, 425 mentioned both the height and weight of the consumer, allowing a calculation of body mass index (BMI), which is measured in kilograms per meters squared. A BMI over 25 indicates a person is overweight.[24] Of the 425 reports with known BMI, 217 (51.1%) involved consumers who were overweight and 208 (48.9%) involved consumers who were not. Among cardiac reports, neurologic reports, and psychiatric reports, the percentages of consumers with known BMI who were not overweight were 50.5%, 44.4%, and 37.5%, respectively.

C. Metabolife's Handling of the Adverse Event Reports Exhibited Indifference

An examination of the adverse event reports reveals that Metabolife adopted a careless approach to consumer complaints of significant adverse health effects, apparently failed to seek essential follow-up information from consumers, and failed to report serious adverse events to FDA.

1. Metabolife Adverse Event Reports Were Often Handwritten and Incomplete

Many of the adverse event reports were carelessly compiled and incomplete. For example, nearly one-third of the reports of significant adverse events (30.6%) were handwritten. These handwritten reports were often illegible in parts and confusing, as shown with several examples in Apendix A.

Large numbers of the reports, whether handwritten or typed, omitted basic data. Over

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[23]Age was known in 783 cardiac reports, 26 neurological reports, 151 psychiatric reports, and 45 of the most serious reports, including heart attack, seizure, stroke and psychosis.

[24]*Body Mass Index For Adults* (on line at www.cdc.gov/nccdphp/dnpa/bmi/bmi-adult.htm).

half of the reports of significant adverse events (1,071 reports or 53.9%) did not include the age of the consumer. Over two-thirds of these reports (1,347 reports or 67.9%) omitted gender, and over one-third (664 reports or 33.4%) did not have a legible date. In total, nearly 90% of the reports of significant adverse events (1,698 reports or 85.5%) were missing gender, age, or date.

Even the reports of the most serious adverse events were carelessly compiled and incomplete. Among the reports involving heart attack, stroke, seizure, or psychosis, 44.3% were handwritten, 53.9% omitted age, 41.6% omitted gender, and 30.3% did not have a legible date. In total, 74.2% of these reports were missing gender, age, or date.

2. Metabolife Failed to Seek Medical Records Needed to Investigate Significant Adverse Events

The adverse event reports virtually never document a request by Metabolife for medical records needed to evaluate the safety of its product. Of the 1,985 reports of significant adverse events, there is evidence that Metabolife requested medical records for further investigation or obtained such records as followup to a consumer complaint in only 29 cases (less than 2%). Metabolife obtained records in only 14 of these cases (less than 1%).[25]

Even where there are unmistakable "red flags" implicating its product in a serious medical condition, the reports rarely mention any request by Metabolife for follow-up medical records. In 128 of the adverse event reports, the consumer was hospitalized or required emergency room care. Yet in only 13 of these cases (10.2%) do the reports note that Metabolife requested medical records or did the company otherwise obtain them. In 63 of the adverse event reports, the consumer indicated that his or her doctor indicated that Metabolife's products may have caused the adverse health effects. Yet in only seven of these cases (11.1%) do the reports note that Metabolife requested the doctor's medical records or did the company otherwise obtain them.

Metabolife also appears to have failed to conduct responsible follow-up when consumers reported the most serious adverse events. Among the adverse event reports involving heart attack, stroke, seizure, and psychosis, there is documentation in the reports that Metabolife requested additional medical records or that the company obtained them in only 4.5% of the cases.

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[25]According to Metabolife, the company obtained the medical records of 46 consumers. Metabolife, Index of Redacted Customer Records with Corresponding MIPER Numbers (October 2002). Most of these records related to consumer complaints of nausea and other conditions that were not considered in this analysis of significant cardiac, neurological, and psychiatric symptoms or could not be linked to one of the adverse event reports submitted by the company.

3. Metabolife Waited Years to Notify FDA of Adverse Event Reports that Drug Manufacturers Must Refer to FDA Within 15 Days

Manufacturers of drugs are required to report certain serious adverse events to FDA. Although manufacturers of dietary supplements are not legally subject to the same requirements, their products can contain substances that produce powerful pharmacological effects and potential toxicity similar to those of drugs. For this reason, the report compared Metabolife's recording and reporting of adverse events to the standards applicable to drug manufacturers.

According to FDA rules, manufacturers of drugs must report to FDA all "serious and unexpected" adverse events within 15 days.[26] Serious adverse events are defined as:

> Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.[27]

Examples of "serious" adverse events cited in FDA's regulations include conditions requiring "intensive treatment in an emergency room" and "convulsions that do not result in inpatient hospitalization."[28] Drug manufacturers are required to send these adverse event events to FDA even if the companies do not believe that the drugs caused the problems.

In the case of Metabolife's products, the FDA definition of "serious" events would, at a minimum, include any adverse event reports involving death, hospitalization, seizure, stroke, and heart attack.[29] For the three types of reports covered in this analysis -- significant cardiac, neurological, and psychiatric reports -- these categories collectively include 114 reports. Under FDA's drug regulations, all of these adverse event reports would have been required to be submitted to FDA within 15 days.

Metabolife, however, submitted none of these adverse event reports within 15 days. Of these adverse event reports with legible dates, 80 were known more than a year before they were submitted. Seventy-five of these were known more than two years, and 36 were known to Metabolife more than three years before they were submitted to FDA in August 2002.

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[26] 21 CFR 310.305

[27] 21 CFR 310.305

[28] 21 CFR 310.305

[29] For drugs, manufacturers must only report within 15 days those serious events that are "unexpected." The term "unexpected" is defined with reference to the FDA-approved label, which does not exist for Metabolife 356.

Metabolife's recordkeeping for these adverse events also would not meet standards for adequate recordkeeping under FDA's drug reporting requirements. While drug reports must include date, gender, and age, only 32 of the 114 reports (27.8%) included all of this information.

D. Metabolife's Adverse Event Reports Contradict Metabolife's Claim that It Was Unaware of Consumer Problems

As discussed in part I, Metabolife informed FDA on repeated occasions that it had no knowledge of consumer complaints of adverse health effects. As late as February 1999, the company's chief counsel informed FDA:

> Metabolife has never been made aware of any adverse health events by consumers of its products. Metabolife has never received a notice from a consumer that any serious adverse health event has occurred because of ingestion of Metabolife 356.[30]

The adverse event reports submitted by Metabolife conflict with these statements. Many of the reports of significant adverse events were received by Metabolife prior to its statements to FDA. Among the significant adverse event reports with legible dates, 138 reports were received by Metabolife before February 1999. These reports include 12 cases of heart attack, seizure, stroke, and psychosis, examples of which are shown in Apendix B.

E. Interpretation of Findings

The findings in this report should be considered minimum estimates. The poor quality of Metabolife's adverse event reports means that the number and severity of the actual adverse events reported to Metabolife could be greater than revealed on the forms compiled by Metabolife. For example, because many of the significant adverse event reports do not contain a legible date, the number of reports received by Metabolife prior to February 1999 could be greater than found in this report. Similarly, because Metabolife did not consistently collect information on hospitalizations or emergency room visits, the number of adverse event reports involving hospitalizations or emergency room visits could be greater than found in this report.

In addition, thousands of consumers reported adverse events that did not involve cardiac, neurologic, or psychiatric problems, such as severe allergic reactions. These adverse event reports were not analyzed in this report.

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[30]Letter from Allen P. Beinke, Counsel for Metabolife, to FDA Docket No. 98N-0148 (Feb. 9, 1999).

IV. CONCLUSION

Metabolife has long been aware of nearly 2,000 reports of significant adverse events involving consumers of its products, but it denied to FDA that it had received any such reports. These reports include reports of heart attacks, strokes, seizures, and even death. Contrary to assertions by Metabolife, many of these adverse event reports involved healthy individuals taking recommended dosages. Moreover, Metabolife handled these reports in a careless manner, omitting basic information in its reports and failing to follow up by obtaining essential medical records.

Addendum A:

Examples of Handwritten Adverse Event Reports

Want to know why

diff. breathing

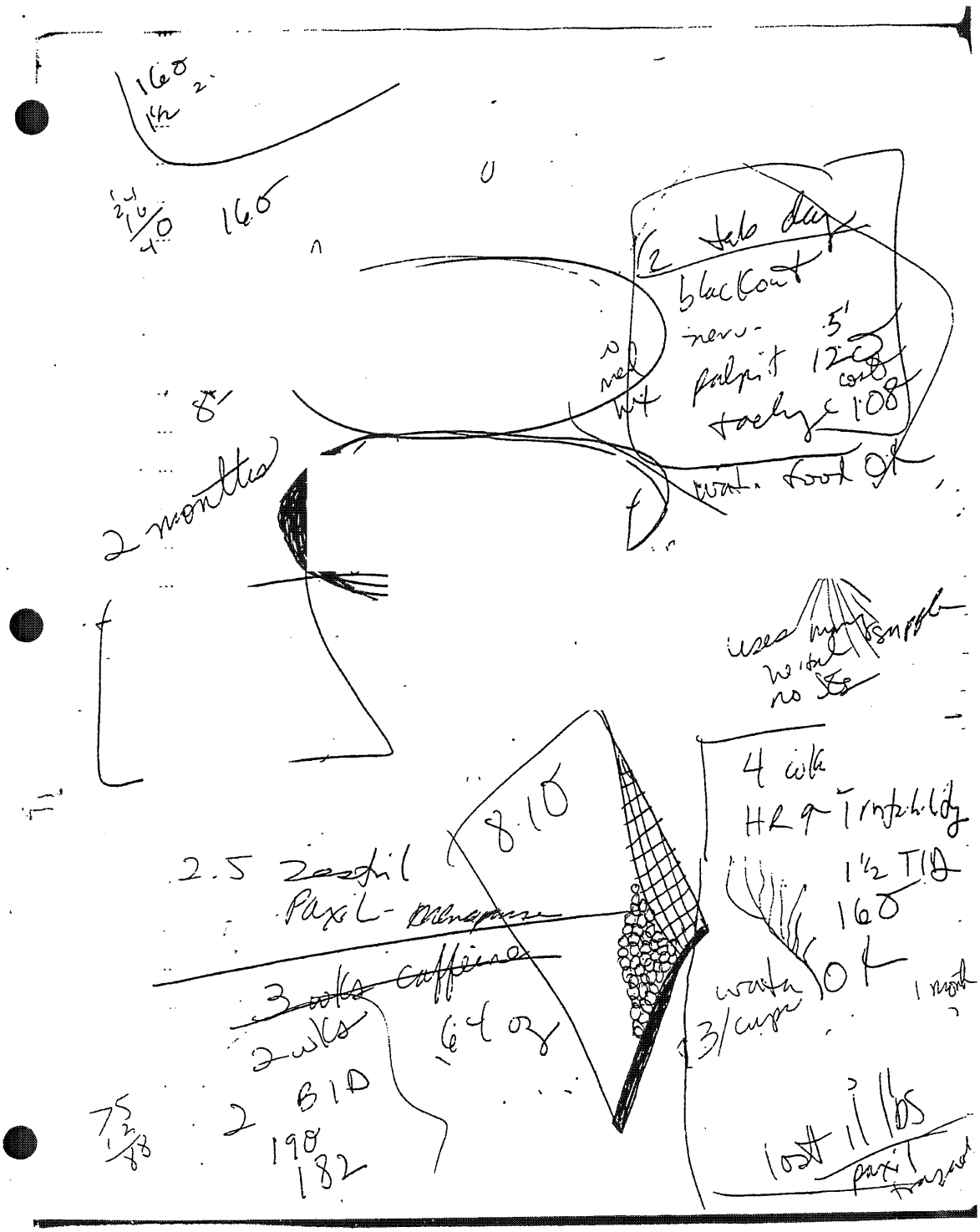
EKG ok
bloods ok

CP
dysphagia
ER - doc said ret.

19 yo ∅ med prob.
130 # 5'6"
Sun - ↓10 lbs
→ Wed. pain on H2O eating

∅ lost #

4% -
dehydrated
still has CP, etc.



21

Monday
September
1998

7:00
7:30
8:00
8:30
9:00
9:30
10:00 3 months
10:30
11:00
11:30
12:00
12:30
1:00
1:30 heart attack
2:00
2:30
3:00
3:30
4:00
4:30
5:00

CONFIDENTIAL
REDACTED

Addendum B:

Examples of Serious Adverse Event Reports
Received by Metabolife Before February 1999

Glenda Aspholm

From:
Sent: Monday, April 27, 1998 6:39 PM
To: info@metabolife.com
Subject: Medical Complication

Importance: High

At 4:30 am on 4/27/98 my wife had a grand mal seizure. After admission to the emergency room of a near by hospital and several test the doctors came to the conclusion that your product was the only likely factor since she had no history of seizures or head injuries. I cannot stress enough the fear I experienced from her sudden convulsions that awakened me in the early morning hours, for I was sure she was experiencing a fatal stroke or cerebral hemorrhage. Another alarming revolation at the hospital was that Metabolife showed up as an amphetamine in her urinalysis. Please help us by providing any detailed testing on your product and any know side effects that have been reported, especially any similar to our experience. I'm am well aware of the legality of your product so please don't hide behind this, help us, her experience could occur again.

JMR 9/15/05

1:52 P.M. # 8014
= 25 YRS. FEB. HAD STROKE
ALSO A STUDENT. 195 LBS. 5'9

Date 9/28/98 **Medical Log Notes**

(1873)

Name
Phone _____
Age 23
Weight 135#
Height 5'6
Medications ~~0~~
_____
_____
_____

Gender ☐ Male ☒ Female

Chief Complaint

1. No Weight Loss
☐ Underdosing ☐ Med. Conflict
☐ Dehydration ☐ Other _____

2. Side Effects
☐ Jitteriness/Nervousness ☐ Insomnia
☐ Cramping ☐ GI Disturbance
☐ Other _____

Medical History 6mos - stroke - last week - MD's said Mathuang.
lost 30-35#

Conclusion/Recommendations: _____

Current Dosage 6/D **Recommended Dosage** _____