



*Advancing the Understanding
of the Disease of Obesity*

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Division of Dockets Management (HFA-305)

Food and Drug Administration

5630 Fishers Lane Rm. 1061

Rockville, Md. 20852

Re: FDA Guidance Document on Weight Loss Drugs
Docket No.2003D-0570

On January 31, 2003, the Food and Drug Administration (FDA) issued the paper, Improving Innovation in Medical Technology: Beyond 2002 indicating an interest in reviewing the Guidance for the Clinical Evaluation of Weight Loss Drugs (issued September 24, 1996). During this time, the Secretary of the Department of Health and Human Services, Hon. Tommy Thompson, and the Commissioner of the Food and Drug Administration, Mark McClellan, were directing public attention and internal resources to the burgeoning problem of obesity in America.

After issuance of the FDA paper, the American Obesity Association (AOA) convened a meeting of pharmaceutical companies involved in the development of drugs for the treatment of obesity. The meeting was held in April 2003 in Washington, D.C. and was addressed by Dr. Lester Crawford, then Deputy Commissioner of the FDA.

That meeting addressed issues of common interest to those engaged in the development of drugs to address the obesity epidemic. A number of specific problems with the 1996 guidances were identified. Subsequently, drafts of suggestions for changes in the 1996 guidelines were circulated for comment within the group. A second meeting of companies was held in October 2003 in Florida and to discuss revisions to the draft. A second draft of changes was circulated to which several companies responded. A writing committee was assembled to integrate suggestions into a final draft. The companies involved in this consultative process are Abbott Pharmaceuticals, Amylin Pharmaceuticals, Eli Lilly & Company, GlaxoSmithKline, Johnson & Johnson, Merck Research Laboratories, Millennium, Novartis Pharmaceuticals Inc., Pfizer Inc., Regeneron Pharmaceuticals Inc, Roche Laboratories, and Sanofi-Synthelabo Inc. (Not every company participated in every meeting.)

2003D-0570

C1

A note should be made about these topics and recommendations. The AOA-industry group tried to identify those issues about which there was general agreement on the need for change. It was recognized that each company might have concerns, which are addressed in this document and others which are not addressed. This is not to diminish the importance of the issues which are not herein addressed. Rather, this document is intended only to highlight those issues on which there is widespread agreement within the AOA-industry group. It should also be noted that, even though there was agreement in general on these issues, there was no absence of debate. There was vigorous give-and-take on many issues and a recognition that reasonable people may disagree. Our intention is to take this discussion to critical decision-makers at the Food and Drug Administration and the National Institutes of Health (NIH) for their informed consideration.

On January 26, 2004, the Food and Drug Administration issued a Request for Comments on a Draft Guidance on the Clinical Evaluation of Weight-Control Drugs. (Docket No. 2003D-0570. This cover letter and attached draft changes are submitted to the docket in the interest of the broadest public debate on this important issue.

A. The Perception of Risk-Benefit Drugs in General for the Treatment of Obesity

The history of drugs for the treatment of obesity is an unfortunate one. Early medications too often proved to be so unsafe to be removed from the market. This experience has colored the thinking of many dispensing physicians, consumers and the general public. Unfortunately, experiences with previous weight loss drugs have created a negative perception of the utility of any future drug to treat obesity.

The currently approved medications for the treatment of obesity are demonstrating safety and efficacy but there are only two such products, giving physicians and patients few options.

In general, the biomedical research and drug development community agrees with the FDA, indeed the whole of the Department of Health and Human Services, that obesity is an urgent public health issue which requires more options for medical intervention. There are millions of cases where drug intervention might be employed to reduce weight or body fat and the conditions caused by excess weight or fat. In addition, the pharmaceutical industry is excited about recent scientific discoveries, which have greatly elucidated the mechanism by which body weight is regulated. These findings have indicated several new, potential therapeutic targets that hold a promise of greater efficacy and safety than past products.

It is felt that the negative perception of drugs to treat obesity is widespread at the FDA and affects the approval process.

- Where the researchers on obesity medicines sees millions of cases of very sick persons who need to lose weight to improve their health (e.g., there are over 8 million persons with morbid obesity alone), the FDA is perceived as anticipating

that any weight loss drug will be widely used by persons who are not overweight or obese or who desire cosmetic weight loss only or will be widely abused.

- Where these researchers see many individuals unresponsive to diet and physical activity intervention, they perceive that the FDA as seeing diet and physical activity as the optimum strategy to improve all or almost all cases of excess weight.
- Where the researchers on obesity medicines see many drugs carrying as significant health risks as obesity medications, they perceive the FDA as holding weight loss drugs to a higher standard of safety.

In short, the obesity pharmacology development field sees the FDA as historically being resistant to medications to treat obesity. This is, of course, a significant concern to any company that must decide whether to allocate millions of dollars to development of a drug for obesity or some other condition. FDA's public acknowledgement of the importance of developing safe and effective drugs to address obesity and its associated morbidities is viewed as important first step in alleviating the AOA-industry group's concerns. Important progress will be made when this publicly announced change in perception is reflected in the new guidance document. An important suggestion along these lines is reflected in new language regarding Endpoints which acknowledges that changes in obesity-associated cardiovascular risk factors, both positive and negative, are valuable for determining the risk-benefit ratio of any one product. And that labeling for such important risk factors can be obtained in association with weight loss rather than independent of weight loss as presently dictated by the FDA.

B. Clinical Issues Affecting Obesity Drug Approval

The AOA-industry working group has developed a proposed draft of a guidance for weight loss drugs. Among the features of the proposed new guidance are:

1. A change in the title from drugs for weight loss to drugs for treatment of obesity and overweight.
2. The proposed draft is more descriptive of the disease process of obesity.
3. The proposed draft proposes acknowledging the public health importance of prevention of weight regain after loss and long term weight loss maintenance.
4. The proposed draft contains a new section on potential therapeutic interventions.
5. The proposed draft combines population requirements into one section.
6. The proposed draft would lower the BMI threshold from 27 with one or more comorbid conditions to a BMI of 25 with one or more comorbid conditions.
7. Language describing requirements for Phase I, II and III studies is made more congruent with guidances for other diseases.

8. The requirement that all subjects on Phase II and Phase III studies receive instruction in diet, exercise, behavior modification and other life style changes is modified to require that diet and exercise instruction is defined and standardized.
9. The requirement for a six-week run-in period where all subjects are encouraged to partake of a diet restricted and increase exercise intervention is deleted. It is felt that this requirement may skewer the results of the trial and not reflect real world conditions.
10. The proposed draft increases from two to three the possible demonstrations of efficacy. The three are:
 - i. The drug effect is statistically significantly greater than placebo and the mean associated weight loss exceeds the mean placebo by 5% at the end of twelve months.
 - ii. The proportion of subjects who reach a loss of 5% is significantly greater than placebo at the end of one year.
 - iii. The proportion of subjects who maintain a loss of at least 5% is significantly greater in subjects on drug than those on placebo at the end of two years.

The proposed draft also acknowledges an important public health role for putative drugs which would maintain weight loss which has been achieved by other means. It was felt that this was a potentially valuable, although speculative, therapeutic area.

Finally, the AOA-industry group would prefer that the relevant end-points should reflect a medically significant loss of body fat. However, there is no consensus on what is a medically significant loss of body fat at this time. We urge the Food and Drug Administration and the National Institutes of Health to cooperate on developing the research on what is a medically significant loss of body fat and to achieve consensus on a new standard.

The AOA and industry look forward to an ongoing dialogue with the FDA and NIH as new guidances are developed.

Sincerely,



Morgan Downey
Executive Director

1 **GUIDANCE FOR THE CLINICAL EVALUATION OF ~~WEIGHT-CONTROL~~**
2 **DRUGS FOR THE TREATMENT OF OBESITY AND OVERWEIGHT** ~~(9-24-96)~~

3 **1. INTRODUCTION**

4 This guidance is intended to recommend clinical trials and clinical drug development
5 programs that will provide acceptable demonstrations of the safety and efficacy of drugs
6 to treat individuals who have are obesity or areand overweight. ~~improve health and self-~~
7 ~~esteem by reducing body-fat.~~ General guidelines for conduct of clinical trials (GCP) and
8 for development of new drugs for marketing should be followed in developing such
9 ~~weight-control~~ drugs. Only those aspects of the trials that are specific to such weight-
10 ~~control~~ drugs will be discussed in this document. Refer particularly to the Guidelines for
11 the Format and Content of the Clinical and Statistical Sections of New Drug
12 Applications.

13
14 These guidelines are intended to present desirable approaches rather than mandatory
15 standards. In part, they contain recommendations for clinical studies which are
16 recognized as valid desirable approaches to be used in arriving at conclusions concerning
17 safety and efficacy of new drugs; and in other part, they reflect the views of experts in the
18 field as to what constitutes appropriate methods of study of specific classes of drugs. In
19 some cases, other methods may be equally applicable or newer methods may be
20 preferable, and for certain entirely new entities it is possible that the guidelines may be
21 only minimally acceptable. Sponsors are encouraged to discuss approaches with staff of
22 the Food and Drug Administration.

23
24 **2. GENERAL RATIONALE**

25 ~~Excess weight is associated with excess morbidity (diabetes, hypertension, coronary heart~~
26 ~~disease, stroke and other cardiovascular diseases, hyperlipidemia, osteoarthritis, several~~
27 ~~types of cancers, gall bladder disease, sleep apnea, depression, and low self-esteem) and~~
28 ~~mortality. It seems likely that preventing obesity, and/or losing weight, might prevent or~~
29 ~~reverse at least some of these morbidities. Weight is frequently (usually) regained~~

30 ~~the drugs have been discontinued. Certain drugs might maintain weight loss successfully~~
31 ~~in some individuals if drug administration were continued for longer periods of time.~~
32 ~~Since it is possible that a new "set point" will be developed at a reduced body mass, drug~~
33 ~~administration might be required for only a limited time; however, it is probable that drug~~
34 ~~administration must be continued indefinitely in order to reap the health and other~~
35 ~~benefits of reduced body weight. FDA standards for weight control drug approval~~
36 ~~anticipate the investigation of long term safety and efficacy of weight control drugs,~~
37 ~~leading to approval of drugs with indications for weight control using long term or~~
38 ~~indefinite drug administration.~~

39 Obesity is a long term, chronic, fatal and relapsing disease in which the principal sign is
40 excess adipose tissue. Obesity is a phenotypic disease that has primary etiologies (e.g.
41 "primary obesity", hypogonadotropic hypogonadism, Prader-Willi syndrome),
42 secondary etiologies (e.g. Cushing's disease, hypothyroidism) and may even be drug
43 induced. The etiology of "primary obesity" is multifactorial. Increased adiposity is
44 caused by genetic, environmental, behavioral and hormonal factors. It has been
45 established that there are neuroendocrine factors that affect body mass, appetite, and
46 satiety.

47 Excess adiposity alone causes a number of changes in the body's lipids metabolism.

48 Obesity significantly affects the musculoskeletal and cardiovascular systems.

49 Obesity is well established as a cause of many important health conditions (referred to as
50 comorbid conditions) including type 2 diabetes, heart disease, hypertension, stroke,
51 dyslipidemia, metabolic syndrome, sleep apnea, osteoarthritis of the knee and hip and
52 some cancers. Obesity is strongly associated with numerous, other adverse health
53 conditions, including but not limited to depression, reproductive disorders including birth
54 defects, reduced quality of life and psychosocial problem. Obesity is known to be the
55 second leading cause of preventable deaths in the United States and may exceed tobacco
56 smoking as the leading cause in the near future.

57 Obesity has reached epidemic proportions in the United States not only among adults but
58 among children and the elderly as well. Over 30% of adult Americans and 15% of
59 children and adolescents are obese. The rates of obesity are also increasing among the
60 nation's children and adolescents. This trend is especially troubling are the adverse

91 To achieve one or more of the above goals, single drugs or drugs in combination may act
92 act on one or more mechanisms that promote excess adiposity. These may include
93 reduction of hunger/appetite, enhancement of satiety, alteration in food preferences,
94 enhancement of physical activity, increases in energy expenditure or enhancement of fat
95 oxidation. In addition to the known mechanisms of increased adiposity listed above, a
96 drug may be targeted at novel mechanisms or strategies that are at this time are unknown.
97

98 **4. Population**

99
100 For most weight control obesity and overweight drug studies, subjects in long-term
101 clinical trials should be moderately to markedly obese with have a body mass index
102 (BMI) of at least 30 kg/m² or greater for otherwise healthy individuals, or a BMI at least
103 25 kg/m² or greater in individuals for with one or more comorbid conditions (such
104 as those described in Section 2). It is of interest to identify obesity by methods that
105 measure percent body fat and fat distribution. Drug developers may use any scientifically
106 acceptable measurement definition. Type of obesity (peripheral or central, as indicated by
107 measures of central obesity, such as waist hip ratio or sagittal diameter), presence and
108 severity of risk factors and related co-morbidities, severity of obesity, and duration or age
109 at onset of obesity may be factors that should be selected, excluded or stratified. Ideally,
110 the population will include minorities and both sexes in numbers adequate to allow
111 measurement of response separately in men and women, and in blacks, caucasians, and
112 hispanics. Methods used to recruit subjects for obesity drug trials should be noted.
113 Demographic data appropriate to the target population should be obtained. If relevant to
114 the desired indication, population might include children, adolescents, the adult
115 population, both genders, the elderly or racial, gender, and ethnic groups. Therapy for
116 specific etiologies of obesity (e.g. hypogonadotropic hypogonadism, Prader Willi
117 syndrome) may be considered for certain medicines.

120 ~~subjects~~ subjects who are otherwise free of other diseases. It is desirable to include
121 minorities (blacks and Hispanics in particular) and both males and females in the
122 clinical studies. These clinical studies include the earliest studies of safety, tolerance
123 tolerability, pharmacokinetics (if applicable), pharmacodynamics, mechanism of action,
124 and dose determination. The mechanism of action of the drug should be established if
125 possible.

126

127 6. DOSE RANGE FINDING PHASE II STUDIES

128 Because a drug for weight loss may be prescribed extensively for relatively healthy
129 subjects, it is particularly important that the drug dose recommended not be excessive.
130 Dose finding should identify the lowest dose of the drug that safely achieves an optimal
131 drug effect. Inclusion of at least 3 doses of drug in dose finding efficacy studies will
132 probably allow identification of a low dose that is inadequate, and also a dose that
133 achieves the maximum benefit that can be obtained without toxicity. Phase II trials
134 should be designed to obtain guidance for the design of Phase III trials and to validate
135 proof of concept in a small number of affected individuals. The goals of Phase II studies
136 are to capture information on safety, efficacy and dose response in the target population.
137 They should obtain working estimates of the nature and severity of the most common
138 side effects commonly associated with the new product. Patient history may include a
139 number of factors, such as family history, alcoholic intake, tobacco use, exercise/activity
140 level and dietary habits. Dietary and activity regimens should be defined and
141 standardized within a trial and as appropriate for the patient population. Trials
142 should usually be randomized, double-blind, and placebo controlled, with all subjects,
143 both on drug and placebo, receiving similar instruction in diet, exercise, behavior
144 modification and other life style changes, such as use of tobacco and alcohol. This does
145 not mean that all studies must be conducted in patients that are practicing these life style
146 changes, but that in all studies instructions on life style should be similar in drug and
147 placebo groups. Generally, subjects should be moderately to markedly obese (BMI at
148 least 30 is suggested; other obesity measures may be preferred) but subjects may be
149 healthy otherwise. The population should include minorities and both sexes if the target

150 population is, broadly, overweight Americans. It is likely that 3-6 month studies in about
151 200 subjects will be required to show preliminary efficacy of the drug, but actual number
152 depends on the amount of difference observed between the efficacy of drug and of
153 placebo.

154

155 7. TRIALS TO ESTABLISH EFFICACY PHASE III TRIALS

156 Trials to establish the safety and efficacy of a weight loss drug for the treatment of
157 persons with obesity and overweight should be randomized, double-blind, and placebo-
158 controlled. Dietary and activity regimens should be defined and standardized within the
159 trial as much as possible in the population, with all subjects, whether on drug or placebo,
160 receiving similar instruction in diet, exercise, behavior modification and other life-style
161 changes. For the long-term efficacy studies, it is preferable to instruct all subjects in the
162 relevant life-style modifications. . Patient history may include a number of factors, such
163 as family history, alcoholic intake, tobacco use, exercise/activity level and dietary habits.
164 Dietary and activity regimens should be defined and standardized within a trial and as
165 appropriate for the patient.

166

167 5.1 Population

168 ~~For most weight control drug studies, subjects in long-term trials should be moderately to~~
169 ~~markedly obese with body mass index (BMI) at least 30 for otherwise healthy~~
170 ~~individuals, and BMI at least 27 for those with comorbid conditions (hypertension,~~
171 ~~hyperlipidemia, glucose intolerance, cardiovascular disease, sleep apnea, or other~~
172 ~~obesity-related conditions). However, BMI does not distinguish size that is due to bone~~
173 ~~and muscle from that due to fat, nor does it identify subjects with visceral obesity, a~~
174 ~~potent predictor of morbidity. It is often preferable to identify obesity by methods that~~
175 ~~measure body fat and its distribution.~~

176

177 ~~Type of obesity (peripheral or central, as indicated by measures of central obesity, such~~
178 ~~as waist-hip ratio or sagittal diameter), presence and severity of risk factors and related~~
179 ~~co-morbidities, severity of obesity, and duration or age at onset of obesity may be factors~~

180 ~~that should be selected, excluded or stratified. Ideally, the population will include~~
181 ~~minorities and both sexes in numbers adequate to allow measurement of response~~
182 ~~separately in men and women, and in blacks, caucasians, and hispanics. Methods used to~~
183 ~~recruit subjects for obesity drug trials should be noted. Race, socioeconomic status, and~~
184 ~~education should also be included in demographic data.~~

186 5.2 Procedures

188 A. Subject Selection.

189
190 ~~Subjects who meet the entry criteria with regard to obesity and risk factors may be~~
191 ~~entered into a program aimed at weight reduction, but without drug. Such a program~~
192 ~~might include calorie restricted or controlled diet, behavior modification, and exercise.~~
193 ~~As a minimum, a modestly restricted diet and regular exercise should be actively~~
194 ~~encouraged.~~

195 ~~Placebo may be used during this period so that placebo responders are identified.~~
196 ~~Generally, this program should be continued for 6 weeks. Subjects should not be placed~~
197 ~~on drug as long as weight loss continues without drug, but may be randomized when~~
198 ~~weight has plateaued, as long as their weight remains above their goal for weight~~
199 ~~reduction (e.g. ideal body weight). Although subjects who are still losing or who reach~~
200 ~~ideal body weight on this program have no need for drug at that time, they may be kept~~
201 ~~on the weight program and randomized to placebo or study drug later if their success at~~
202 ~~weight loss evaporates. It is possible that the principal benefit of drug over placebo will~~
203 ~~be in maintaining weight loss. In this case, the studies that are of sufficient duration to~~
204 ~~detect a difference between drug and placebo in long term maintenance of a loss obtained~~
205 ~~with the drug of interest or with other modalities (very low calorie or formula diet,~~
206 ~~intensive diet and exercise, etc.) will be most useful for demonstrating efficacy and for~~
207 ~~dose determination.~~

209 7.1 B. Endpoint evaluation.

210 Actual weight loss should be reported, ~~and, also,~~ It is helpful to express weight loss in
211 relative terms such as per-cent of initial body weight ~~or percent of excess over ideal body~~
212 ~~weight~~ or change in body mass index. It is preferred that the product show a loss of body
213 fat compared to placebo in at least one trial but weight is an appropriate surrogate for
214 body fat. Measurement of change in central obesity is also useful.

215 At least ~~two~~ three weight-loss demonstrations of efficacy are possible:

216

217 1. demonstration that the drug effect is statistically significantly greater than the placebo
218 effect and the mean drug-associated weight loss exceeds the mean placebo weight loss by
219 at least 5% for the last month at the end of one year compared to original body weight or
220 a comparable amount of body fat.

221

222 2. demonstration that the proportion of subjects who reach and maintain a loss of at least a
223 a loss of 5% of their initial body weight is statistically significantly greater in subjects on
224 drug than in those on placebo at the end of one year.

225 3. demonstration that the proportion of subjects who maintain a loss of at least 5% of
226 their initial body weight is significantly greater in subjects on drug than in those on
227 placebo at the end of two years.

228

229 Changes in risk factors or in waist to hip circumference or sagittal diameter may be
230 appropriate endpoints depending on the population to be studied. Delay in the onset
231 Development of diabetes, dyslipidemia, hypertension, cardiovascular events, osteoarthritis
232 or other complications of obesity (See Section 2) may be a suitable endpoint in certain
233 eases are desirable endpoints but not required for registration.

234 Measurement of obesity-associated cardiovascular risk factors (e.g. lipids, blood pressure
235 and glucose tolerance, type 2 diabetes) during drug administration may be encouraged,
236 as they may have a place in determining the balance of benefit vs risk for the drug. If one
237 or more of these factors deteriorates or is not improved, the risk associated with this
238 deviation must be considered in making a benefit-to-risk decision for the drug. Likewise,
239 a drug may demonstrate both weight loss and reduction in obesity-associated
240 cardiovascular risk factors mentioned above. Improvements in such factors must be

241 considered in making a benefit-to-risk decision for the drug and should be described in
242 the label as a benefit of the drug.

243

244 It may be advantageous to determine effects of drug induced weigh loss on quality of life
245 and related factors. Favorable changes in risk factors and quality of life may be
246 mentioned in the package insert and might lead to an indication for risk factor alteration.

247 The effect need not be independent of weight or fat loss. Treatment of hypertension,
248 lipids or type 2 diabetes may be a suitable indication.

249 ~~It may be advantageous to determine effects of drug induced weight loss on quality of~~
250 ~~life and related factors. Favorable changes in risk factors and quality of life may be~~
251 ~~mentioned in the package insert and might lead to an indication for risk factor alteration.~~
252 ~~Treatment of hypertension or type 2 diabetes may be a suitable indication.~~

253

254 Weight loss achieved with calorie restriction alone is usually associated with loss of both
255 fat and muscle tissue. Exercise has been reported to reduce or eliminate muscle loss. A
256 carbohydrate-restricted regimen will usually result in loss of body water. For these
257 reasons, it may be desirable in a suitable number of patients and in at least one trial, at the
258 start of the trials, to establish that the subjects have excess body fat by one or more of the
259 accepted measurements, such as skin fold thickness, body circumferences or sagittal
260 diameter, under-water weighing, bioelectric impedance, ~~and~~ DEXA, CT scan or MRI.

261 Follow-up measurements can then confirm that body fat is decreased commensurate with
262 the weight loss and that weight loss is not associated with excessive loss of body water or
263 muscle. ~~It may be of some interest to detect any change in visceral obesity, or in the small~~
264 ~~dense LDL that might be present in patients with abdominal obesity.~~

265

266 **7.2 Duration of Trials**

267

268 The duration of clinical trials must be consistent with the selected endpoint. Drugs must
269 be viewed as part of a long-term strategy for weight management. Drugs may be
270 indicated for long-term weight loss and weight maintenance or weight gain prevention.

271 The demonstration of efficacy for long-term drug use, will usually include demonstration

272 that the difference in weigh loss between placebo and active drug effect on weight is
273 maintained for at least 12 months, ~~i.e., the above mentioned (See 5.2 Endpoint~~
274 ~~Evaluation) conditions for demonstrating efficacy continue to 12 months after the~~
275 ~~initiation of treatment.~~ Weight loss maintenance might decrease over time in both drug
276 and placebo groups, even resulting in reversal of efficacy. Unless significant weight loss
277 is maintained for at least 12 months, benefits on health and quality of life may be lost. In
278 order to obtain an adequate estimation of the safety of weight-control drugs for long-term
279 weight maintenance administration, subjects may be rerandomized to active versus
280 placebo and followed for an additional 12 months (total of 2 years) generally, about 1500
281 ~~subjects are expected to complete 12 months with 200-500 of those subjects completing~~
282 ~~24 months of study. Most often the double blind status of the study is maintained for at~~
283 ~~least 1 year, at which time, placebo patients may be switched to drug and followed on~~
284 ~~open label for another 12 months to a total of 24 months for weight and development of~~
285 ~~obesity related morbidities. For those who have dropped out of the study it is usually~~
286 ~~possible to obtain at least telephone contact at 24 months for self-reported weight, and~~
287 ~~morbidities.~~

288

289 It is not intended that this Guidance apply to all possible weight loss drug evaluations for
290 overweight and obesity. Special circumstances will obtain if the populations or endpoints
291 are not those envisioned in the Guidance. For example, it may be desirable to study a
292 non-obese population for prevention of weight-gain, such as during cigarette withdrawal.
293 Such specific indications may be proposed, with the appropriate rationale, to the Division
294 of Metabolic and Endocrine Drug Products in order to obtain input on the proposed drug
295 program.

296

297 As new drug entities with new modes of action are developed, modifications of the
298 Guidance may become necessary and will be considered

299

300 This document is an informal communication under 21 CFR 10.90(b)(9) that represents
301 the best judgment of the Division of Metabolic and Endocrine Drug Products at this time.

302 This document does not necessarily represent the formal position of the Center for Drug