OBESITY DRUG OUTCOME MEASURES

A Consensus Report of Considerations Regarding Pharmacologic Intervention

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This report is a consensus document reflecting the work of the participants listed below. Participants collectively approved the full report, including the findings and considerations, as a fair and complete articulation of their deliberations and conclusions over the dialogue process. The participants attended as individuals, not formal representatives of their organizations. The federal government observers participated in discussions but have not endorsed the report and the report does not necessarily reflect the views of the Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDC), National Institutes of Health (NIH), or Department of Health and Human Services (HHS).

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Glossary of Acronyms

Acronym	Description
BMI	Body-Mass-Index
CDC	The Centers for Disease Control and Prevention
EMDAC	Endocrinologic and Metabolic Drugs Advisory Committee
EOSS	Edmonton Obesity Staging System
ETASU	Elements to Assure Safe Use
FDA	The Food and Drug Administration
IDSA	Infectious Disease Society of America
IWQoL	Impact of Weight on Quality of Life
NIH	The National Institutes of Health
PDUFA	Prescription Drug User Fee Act
PRO	Patient Reported Outcome(s)
QoL	Quality of Life
REMS	Risk Evaluation and Mitigation Strategies

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Introduction and Project Description

Despite increasing resources aimed at improving diet and physical activity, obesity continues to be one of the most significant public health challenges facing the United States. Based on body mass index (BMI), an indirect measure of one's body fat calculated by weight and height, one in three adults are classified with obesity and an additional one in three are overweight.[†,1]

The scientific evidence supports that obesity is a complex and multifactorial condition with numerous underlying environmental and genetic contributors, as well as many health consequences. Fat tissue acts as an active endocrine organ, producing numerous hormones and other chemical messengers that communicate with the brain and other organs, and contribute to the development or worsening of many illnesses.[2] New evidence suggests that weight gain and obesity lead to hormonal, metabolic, and neurochemical adaptations that may encourage the body to sustain an elevated weight and make weight loss more difficult.[3] Chronic calorie overload may alter key neurologic areas that regulate energy balance. When weight is lost, the body may compensate by altering the central nervous system to lower metabolism and increase hormones that stimulate appetite. Combined, these mechanisms may counter sustained weight loss and may promote weight regain.[4,5] This research may begin to explain why lasting weight loss can be elusive and why obesity defies behavioral treatment in many affected individuals. Knowledge of obesity biology is not widespread and continues to evolve.

In addition to the physiological underpinnings, the causes of obesity have many other contributing factors, making treatment of those with obesity even more challenging, and the need for a range of appropriate approaches to treatment, that much more critical. Because the complexity of obesity has not been well understood, safe and effective treatments have been limited.

While prevention of obesity is a primary goal, the focus of this dialogue was on treatment. This focus is not to imply that prevention is not essential, but for those who are struggling with obesity and suffer from additional health conditions, it is essential to advance their opportunities to access a range of treatments that can assist with reducing their weight and improving their health.

Clinicians and patients have expressed an interest in more options for effective treatment. Pharmacotherapy may be one such option. Some stakeholders question why development and approval of pharmacological interventions for treating obesity have proven so difficult. Others have concerns about health risks to individuals who may use the drugs in unsafe or medically inappropriate ways or who use them appropriately, but experience potentially serious side effects of drugs. For purposes of this report, we define "medically inappropriate use" to mean drug use by those for whom the risks of use outweigh the drug's benefits. Given the sheer number of individuals affected by obesity and those who desire to lose weight, there is potential for a large population to seek out obesity drugs once approved. Rare adverse events, which may not appear in clinical trials, may manifest with wide usage of obesity drugs – as with any drug used by a significant number of patients over a period longer than a clinical trial.

[†] According to the CDC, BMI is calculated by dividing weight in pounds (lbs.) by height in inches (in) squared and multiplying by a conversion factor of 703; a BMI $\leq$18.5 indicates underweight, a BMI 18.5-24.9 indicates normal weight, a BMI 25.0-29.9 indicates overweight, and a BMI$\geq$30 indicates obesity. For the purposes of this report we accept the current parameters employed by the FDA in their Guidance to Industry as a baseline for obesity treatment – that is a BMI $\geq$30 or BMI$\geq$27 accompanied by a weight-related comorbidity implies significant weight-related risk.

Perhaps reflective of a core issue is how these drugs are characterized: weight loss agents vs. obesity treatment. Project participants recognized that a significant concern in making obesity drugs widely available is the possibility of people without obesity using these drugs to lose weight, whether for cosmetic or health-related purposes. The project participants concurred that drugs used to specifically treat obesity should be considered and referenced as "obesity drugs."

As the nation's lead regulatory public health agency, the U.S. Food and Drug Administration (the FDA) plays a number of critical roles with regard to the obesity epidemic, including the review of new pharmaceutical interventions and devices to combat obesity. Approval of new obesity drugs has been limited due to concerns over drug safety and medically inappropriate use, and questions about the benefits of obesity drugs, given the modest 5-10 percent weight loss demonstrated on average with drug use in clinical studies.

Throughout the group discussions, project participants identified several challenges facing the FDA when evaluating the risks and benefits of obesity drugs, which are clustered into three key areas:

- What health or quality of life benefits accrue, beyond weight loss, with drugs for obesity treatment: how are they demonstrated, and does the importance of these benefits vary based on the degree of an individual's obesity and associated risk factors, or the length of time the weight loss is maintained;
- How to evaluate the unique risks associated with the sheer number of people who may seek to use a new obesity drug: from those seeking to address the substantial limitations that obesity places on their feeling, functioning, and survival, to those without obesity who wish to lose weight for cosmetic or other reasons; and
- How to best ensure the safe and effective use of pharmaceutical interventions designed to help those with obesity and most effectively prevent inappropriate use by those for whom the risks of use outweigh the benefits.

The participants deliberated on these challenges and ultimately agreed on several issues described in more detail further on in the report.

Project Description

In an effort to explore the pressing issues and challenges surrounding FDA approval and appropriate use of drugs to treat obesity, The George Washington University School of Public Health and Health Services Department of Health Policy convened the "Obesity Drugs Outcome Measures Dialogue Group," a group of diverse stakeholders who met to identify the key issues surrounding the evaluation of pharmaceutical interventions for the treatment of obesity. These stakeholders attempted to develop a consensus report reflecting those issues and identifying possible solutions. The group met four times in person and participated in a series of working groups and conference calls between November 2011 and July 2012. Members of the group included clinicians specializing in adult and pediatric obesity; leaders from patient and consumer groups; public health organizations and industry representatives; and researchers from academia (see list on page two). Officials from the FDA, CDC, and NIH also observed and provided background information to the group to help inform the process (government officials were not asked to endorse or sign on to this final report). The dialogue process was facilitated by RESOLVE, an independent, Washington, D.C.-based, non-profit organization with more than 30 years of experience facilitating multi-party dialogues on complex, scientifically challenging issues.

Members of the "Obesity Drugs Outcome Measures Dialogue Group" represented interests of those affected substantially by the obesity epidemic, the lack of effective obesity treatments, and the drug approval policies of the FDA. Members were chosen for their experience with treating patients with obesity; familiarity with the policies, science, and care surrounding treatment of patients with obesity; familiarity with the policies around the general issue of obesity prevention and treatment; familiarity with the FDA's drug review and approval process; and willingness to work together in a collaborative, consensus-building process. To foster creative problem solving, members were encouraged to voice their individual viewpoints and ideas. To broaden and strengthen the final report, members were also expected to bring the views of their constituent groups, as well as others with similar interests, to the dialogue process.

By fostering constructive dialogue among this diverse group of stakeholders interested in and affected by the federal process to review and approve obesity drugs, the participants explored many issues and diverse points of view and ultimately reached consensus on the report.

Obesity Background

Obesity is a chronic condition that can affect physical and mental health, as well as quality of life, in numerous ways.[6,7,8,9] Obesity is associated with significantly increased risk of more than 20 chronic diseases and health conditions, including: type 2 diabetes, hypertension, high cholesterol, stroke, heart disease, and cancers.[10,11] Individuals with obesity are also at greater risk for physical symptoms (e.g., joint pain, urinary incontinence), functional limitations (e.g., impaired mobility), and psychosocial problems (e.g., body image disorders, bullying).[12,13,14,15,16,17,18]

Substantial reductions in physical activity and increases in dietary intake have contributed to the increased prevalence of obesity over the past several decades.[19,20] In recent years, public health programs have sought to address the alarming trend in overweight and obesity through prevention efforts, including improving environmental and other factors that increase the likelihood of weight gain. However, for some individuals already struggling with obesity, these important public health initiatives are not sufficient for the weight loss necessary to improve their health. Even as approximately 50-70 percent of adults with obesity are actively pursuing weight loss,[21,22] clinicians and patients express a need for additional interventions.

Currently, persons with obesity who are trying to lose weight have few clinical treatment options, available. Studies have shown that even modest, sustained weight loss of five-ten percent of body weight can result in marked health improvements in some concurrent health-related conditions with, generally, greater weight losses conferring greater benefits.[23,24,25,26,27,28,2930] For some individuals, lifestyle intervention can lead to sustained weight loss and health benefits.[31] Many of these treatments are provided in intensive programs by trained professionals, are not widely accessible to most Americans, and do not address the biological factors that tend to promote weight regain. Similarly, bariatric surgery offers an effective, medically appropriate intervention for some, but not all, patients with severe obesity.

Because behavioral modification and surgery may not address the treatment needs of all patients with obesity, particularly those who have health risks and other health conditions that would benefit from weight loss, clinicians and patients repeatedly express the need for additional treatment options to use *in conjunction with* lifestyle interventions. Pharmacotherapy is one such option. While no treatment options are "silver bullets," pharmacotherapy may serve as a valuable

adjunct to behavior modification to achieve weight loss, facilitate healthier lifestyle habits, and potentially help mitigate biological responses that promote weight regain.

Obesity medications are intended to be used in conjunction with lifestyle changes. They produce weight loss by biologic means to promote and reinforce behavior changes. However, as with any medication, such medications often have effects beyond the promotion of weight loss. Sometimes medications have additional positive health effects; for example, orlistat has an independent effect on cholesterol lowering that goes beyond that achieved with weight loss.[32] Conversely, side effects of medications can produce negative health effects; in the 1990s, fenfluramine, which was used in an unapproved combination with phentermine, called "fen-phen," was found to cause valvular heart disease in some individuals. More recently, Meridia (sibutramine) was withdrawn from the market in 2010 due to increases in cardiovascular disease in some patients. The side effect profile and serious harm of these weight loss medications has led to significant concern and caution among FDA evaluators and advisors over the approval of new obesity drugs. Indeed, before the approval of Belviq (lorcaserin) in June 2012 and Qsymia (phentermine/topiramate) in July 2012, the FDA had not approved a new obesity drug in more than a decade.

Since 2007, the FDA has followed its draft 2007 Guidance for Industry on Developing Products for Weight Management ‡ and considered the recommendations of experts that sit on its Endrocrinologic and Metabolic Drugs Advisory Committee (EMDAC). Under the current Guidance for Weight Management Products, the FDA evaluates drugs intended for the clinical treatment of obesity based primarily on percentage of weight lost and changes in cardiometabolic factors such as blood pressure and lipid levels (see Appendix for additional measures). However, the Guidance does not explicitly include consideration of more symptomatic impairments in patient feeling and functioning such as joint pain, mobility, urinary incontinence, or depression and anxiety, even though the FDA considers such symptomatic improvements in its approval evaluations for some other types of drugs. As a result, companies do not tend to provide data on how a proposed obesity drug affects these types of health conditions and without such data the FDA is unable to consider drug-specific improvements in these additional feeling and functioning domains when making approval decisions.

The FDA is not just concerned with efficacy and tolerability of drugs; the overall impact on health status must be considered in judging the benefits of an obesity medication, not just the medication's impact on weight alone. The FDA has indicated its intent to move toward models of patient centeredness, where patient input and preferences are valued as part of the decision making processes. Under a reauthorized Prescription Drug User Fee Act (PDUFA), the FDA is likely to take a wider, more encompassing look at how drugs developed to treat obesity affect how individuals with obesity feel and function. The FDA is also more likely to include patient-centered outcomes in its risk-benefit framework for evaluating these drugs.

‡ While the current guidance describes these products as drugs intended for weight-management, pharmaceutical interventions should instead be recognized as clinical treatments for obesity.

Findings and Considerations

The rest of the report is structured as a series of "Findings" and "Considerations" grouped into six general categories:

1. Understanding Obesity
2. Characterizing the Population
3. The Need for Additional Treatments for Obesity
4. Limiting or Mitigating the Risk of Medically Inappropriate or Unsafe Use of Obesity Drugs
5. Limitations in the Current FDA Approval Process, and Altering the Risk-Benefit Framework for Evaluation of Obesity Drugs
6. Special Considerations regarding Pediatric Patients with Obesity

The "Findings" are fundamental points that emerged during the Dialogue Group's discussions and should be viewed as informing and essential to the deliberations that resulted in eleven "Considerations."

1. Understanding Obesity

FINDING	Although all factors underlying the increasing rates of obesity are not yet fully understood, scientific evidence suggests that obesity is a complex and multifactorial condition that develops from interplay among biological, genetic, environmental, behavioral, social, cultural, economic and policy factors. New evidence demonstrates that weight gain and obesity lead to hormonal, metabolic, and neurochemical adaptations that may make weight loss more difficult. Obesity has a range of physiological, structural, and functional changes that culminate in health consequences, which can be severe and threaten quantity and quality of life years.

CONSIDERATION	*Pharmacological interventions under investigation for the clinical treatment of obesity should be approached as obesity treatments rather than weight loss agents.*

2. Characterizing the Population

FINDING

The population of individuals with obesity is not homogenous; rather, obesity varies in severity, onset and expression of symptoms, and comorbid conditions. Nonetheless, current characterization of obesity is based primarily on size, as determined by the BMI scale. Some individuals affected by obesity have associated health effects or limitations, while others may have no immediate health consequences or impairments to their daily feeling or functioning. On a spectrum scale, individuals with obesity may fall into at least one of the following three categories based on feeling, functioning and health:

- **Obese and "Well:"** Individuals who carry excess weight but who do not have any comorbidities or risk factors for comorbid conditions and who do not experience any impairments in their daily feeling or functioning.
- **Obese with Risk Factors:** Individuals who carry excess weight who do not yet have any comorbidities, but who have measurable risk factors for comorbid conditions and/or impairments to their daily feeling or functioning.
- **Obese and "Sick:"** Individuals who carry excess weight and who have one or more obesity-attributable comorbidities and impairments to their daily feeling or functioning.

CONSIDERATION

More sophisticated criteria should be employed to characterize individuals at different levels of health, feeling, and functioning impairment, to determine appropriate patient-centered benefits and risks analysis.

COMMENT | On a population level, BMI ≥ 30 correlates well with increased total fat mass and with increased risk for mortality and morbidity, particularly at the extremes of weight. On an individual level, however, BMI is a limited clinical tool. One recently published alternative to BMI, the Edmonton Obesity Staging System (EOSS), takes into account a number of variables beyond BMI alone, such as the presence of symptoms, risk factors, chronic disease diagnoses, and end stage organ disease, and may improve the identification of health risks associated with excess weight.[33]

Using a framework such as that provided in the finding above or the EOSS (refer to Appendix Figure 1 for an example of the EOSS staging tool), regulators could determine how the risks may balance the benefits of a particular obesity drug within the different categories based on feeling, functioning, and health impairments of patients across the obesity spectrum.

3. The Need for Additional Treatments for Obesity

FINDING	A treatment gap exists for those patients who do not respond sufficiently to behavioral and lifestyle interventions and who are not viable candidates for, or do not wish to undergo, bariatric surgery. Such patients need additional options for treatment. Used appropriately, effective prescription drugs could potentially help fill that gap.
CONSIDERATION	*When the FDA determines that the benefits of taking a particular drug outweigh its risks in treating obesity, that drug should be available for clinical use in patients where such use is safe and medically appropriate. Although obesity drugs may not be safe or suitable options for all individuals wishing to use them, it is important that safe and effective drugs be made available as treatment options for individuals with obesity that require an alternative or additional weight loss intervention to diet, exercise, or surgery.*

COMMENT | There is a clear need for safe and effective treatment modalities for obesity. Traditional approaches to lifestyle intervention – exercise, diet and behavioral modification – and other policy measures attempting an environmental impact alone are unlikely to curtail the burden of type 2 diabetes and other obesity-associated chronic diseases. Currently available treatment options may produce modest weight loss for some individuals. However, most weight loss interventions experience high dropout rates and weight maintenance is challenging. A significant proportion of those seeking clinical treatment do not respond adequately to traditional diet, exercise, and/or behavioral modification. Furthermore, as described above, emerging evidence suggests that strong physiological pathways may defend against weight loss and promote weight regain.[34]

4. Limiting or Mitigating the Risk of Medically Inappropriate or Unsafe Use of Obesity Drugs

FINDING	Recognizing the potential for medically inappropriate or unsafe use and serious side effects, obesity drugs should be available only to those patients who meet clinical criteria for use and for whom the benefits of drug therapy for treating obesity exceed the risks of potential side-effects of a particular drug.
CONSIDERATION	*Given the concern over medically inappropriate or unsafe use of obesity drugs by those for whom the risks outweigh the benefits, the FDA could potentially employ a mechanism, such as Risk Evaluation and Mitigation Strategies (REMS) or an alternative, that will allow drug approval, distribution, and use solely for those for whom the drug is indicated.*

COMMENT | While the FDA can approve drugs for specific populations deemed in medical need, the agency is also charged with protecting the public's health and has few mechanisms to restrict medically inappropriate use. In the case of drugs that affect weight, the FDA is legitimately concerned with potential serious side effects and/or medically inappropriate use by both indicated and non-indicated populations. The inability of the FDA to limit medically inappropriate use has created a system where, despite the potential of some drugs to benefit sub-populations, the FDA may reject the drug on the basis of broader population health concerns, and therefore prevent those who could benefit from having access to the drug.

The FDA should explore ways, either through existing or novel mechanisms, to limit off-label prescribing and medically inappropriate use of drugs, while still making available under appropriate conditions drugs that benefit indicated populations.

The REMS program is the FDA's current mechanism for limiting risks associated with the use of certain drugs. REMS was instituted in 2007 to give patients access to drugs with significant risks that would otherwise not have been approvable.[35] REMS have been used to prevent medically inappropriate use through a provision known as Elements to Assure Safe Use (ETASU), which can be used to restrict distribution and/or require provider training. As of July 2011, there were approximately 72 approved REMS, 29 of which included ETASU provisions.[36] However, REMS were not intended to address off-label prescribing and as a result may not be an adequate mechanism to address this issue - one which is not unique to obesity drugs. Limiting off-label use is particularly challenging for drugs where patients for whom the risks outweigh the benefits might frequently seek access to the drug and where providers often prescribe off-label.

One possible alternative to REMS, which was discussed and might warrant further exploration, but which requires further data to determine if it would be effective, was a variant of the Special Populations Limited Medical Use drug class proposed by the Infectious Disease Society of America (IDSA).[37] Under this framework, a drug would be indicated as "not to be prescribed off-label."

In addition to managing patient risks through mechanisms such as those described above, it may also be helpful for the FDA to employ mechanisms that will help patients manage their expectations regarding obesity drug use. A possible tool for influencing prescriber and patient attitudes toward appropriate medical use of drugs lies in the label. Physicians should help patients understand that currently approved and pending obesity drugs might result, on average, in five-ten percent of

weight loss over the course of several months; that the weight loss will plateau; and that continued treatment with the drug does not guarantee sustained weight loss. Such weight loss is not likely to produce dramatic results in physical appearance, but could result in significant improvements in health for those affected with obesity. Obesity drug labels should clearly specify that these are drugs with potentially serious adverse effects that are intended only for the clinical treatment of chronic obesity.

5. Limitations in the Current FDA Approval Process, and Altering the Risk-Benefit Framework for Evaluation of Obesity Drugs

FINDING	Under the current FDA approval process, the risks and benefits of drugs are considered against the entire population for whom the drug is indicated and by whom it could be used. In the case of obesity, that includes those with obesity who experience no other health consequences or impediments to daily living (obese and "well"), and those who experience associated comorbid conditions and whose obesity significantly impacts daily feeling and functioning (obese and "sick").
CONSIDERATION	*Individuals with obesity are not all alike; in evaluating the benefits and risks of obesity-related treatments, patients at different points on the obesity spectrum should be viewed separately. Higher risk of adverse effects of drugs may be acceptable for individuals with more severe obesity and comorbidities. The FDA could consider evaluating the risks and benefits of obesity drugs across several different patient profiles and could tailor approval decisions, combined with risk mitigation strategies described above, to allow access to the drug for those patients with obesity for whom the benefits of the drug outweigh its risks.*

COMMENT | To better account for the varying patient risk profiles across the obesity spectrum, the FDA could use a more patient-centered approach in evaluating the risks and benefits of an obesity drug. Although the health, feeling, and functioning of individuals with obesity vary across the spectrum, for illustrative purposes, those with obesity can be considered to fall broadly within the three different groups described above: those with obesity who are "well," those who are well but with risk factors for other comorbid conditions, and those with obesity who are "sick," meaning that they experience impediments to daily feeling and functioning and have one or more comorbid health conditions.

Across these three broad groups, the level of risk a patient may be willing to accept with an obesity drug will likely vary with how severely their obesity impacts their overall health, daily feeling and functioning, and quality of life. For each group, there might also exist differing available treatment options that could be considered when evaluating the unmet medical need of each group. While lifestyle interventions aimed at dieting and exercise may be successful for some individuals with obesity, for others, the addition of drug therapy could fill a treatment gap and assist with weight loss where other strategies are not working or are not possible due to health or physical limitations, or lack of accessibility.

Applying these concepts to the FDA drug approval process, the FDA may find that certain drugs should be approved for some populations with obesity but not others. For example, the FDA may determine that for those who are obese and "sick," the benefits of taking a particular drug outweigh its risks, whereas this may not be true for those who are obese and "well." By using this framework, the FDA could potentially make drugs with possible serious adverse side effects available to those with significant medical need while limiting or restricting use among other patients, without having to deny approval for the drug across the entire population. To do so, the FDA would need to consider different risk mitigation strategies to ensure that only those for whom it determines the drug to be medically appropriate have access to the drug.

FINDING	While tools exist for measuring the impact of obesity on Quality of Life (QoL) and other Patient Reported Outcomes (PROs), the FDA does not currently accept any QoL or PRO tool for evaluating obesity drug approval applications because the existing tools do not meet FDA regulatory standards.
CONSIDERATION	*To effectively address patient perspectives in making obesity drug approval decisions, tools to measure QoL or PROs that are acceptable to the FDA for regulatory measures need to be developed and utilized in the immediate future.*

COMMENT | While the Impact of Weight on Quality of Life (IWQoL) scale is a widely used scientific measure for changes in quality of life among persons with obesity, the IWQoL, as it is currently constructed, has not been approved by the FDA for regulatory purposes. Other known measures of QoL that assess more global influences do not capture the nuances of obesity's impact on patient experiences such as mobility. A tool that can effectively capture patient perspectives on feeling and functioning is essential.

FINDING	Current FDA Guidance is based primarily on weight loss and changes in cardiometabolic parameters. Relatively less attention is given to alleviation of other health consequences associated with obesity. In the evaluation of the benefits and risks of these drugs, alleviation of symptoms of obesity, such as joint pain and urinary incontinence, and functional limitations, such as decreased mobility, have not been sufficiently emphasized as critical areas affected by obesity, which, in and of themselves, might warrant approval. The FDA's omission of these types of endpoints in the Guidance, coupled with lack of data formally submitted by sponsors and validated QoL instruments, has resulted in limited consideration of these other types of health consequences. Inclusion of these secondary endpoints in the Guidance could provide incentives for pharmaceutical research and development to fully explore improvements in these domains, and improved obesity treatment options.
CONSIDERATION	*The FDA should consider patient improvements in feeling and function associated with weight loss as part of the risk-benefit calculus in its evaluation of drugs for the treatment of obesity where data are provided demonstrating benefit in a drug-specific clinical trial.*
CONSIDERATION	*The FDA should update its Guidance to Industry to include improvements in feeling and functioning domains, for which validated means of measuring such improvements exist, as appropriate and optional secondary endpoints.*

COMMENT | Because obesity can manifest in a wide variety of ways, treatment may result in many health benefits, reductions in symptoms, and improvements in QoL. While some of the consequences of obesity are treatable, others are not. For example, hormone levels that regulate hunger may not adjust to new body weights even a full year after weight loss, whereas mobility or sleep apnea may be significantly improved within this timeframe.[5]

The FDA regularly approves drugs, often with serious adverse effects, as long as they are able to demonstrate improvement in one or more domains of feeling and functioning, and it is determined that the benefits outweigh the risks.

Appendix Table 1 ("Consequences of Obesity") identifies a number of potential consequences of obesity, including commonly considered cardiovascular outcomes, as well as less often considered impairments in feeling and functioning that may be associated with, or impacted by, excess weight, and may (relatively quickly) improve with obesity treatment. The table differentiates "long-term" outcomes, which the current Guidance primarily captures, from "intermediate" and "immediate/symptomatic" outcomes, which the current Guidance does not sufficiently capture. Drug sponsors could use this list to choose potential secondary endpoints for drug-specific clinical trials, and the FDA could then consider data showing the drug's impact on these endpoints in its evaluation of the drug.

Specific feeling and functioning areas that can be measured with validated tools, such as mobility, osteoarthritis, polycystic ovary syndrome (PCOS), or urinary incontinence, should be listed as examples of optional secondary endpoints in the Guidance to Industry. Drug sponsors would not be required to study or show improvement in these areas for approval, but by demonstrating improvement in one or more of these factors, the FDA could consider these additional improvements as benefits when weighing benefits against the risks of the drug. The Guidance should also indicate that the FDA will consider demonstrations of improvement in other feeling and functioning areas not listed when accompanied by drug-specific, validated measures. Many of the measures of improvement in physical, psychosocial, and behavioral health could be included if there were validated QoL tools.

6. Special Considerations Regarding Pediatric Patients with Obesity

While all previous findings and considerations above apply generally to pediatric and adolescent populations, these populations also have a unique set of considerations, as detailed below.

FINDING	Obesity is also prevalent and can be severe across the pediatric and adolescent population. Children and adolescents with obesity are more likely to develop severe obesity as adults. Current treatment options for the pediatric population with obesity are behavior modification interventions, a single prescription weight loss medication (adolescents only), and bariatric surgery. Clinicians are increasingly relying on surgical interventions in extremely obese adolescents. Clinicians need more safe and effective options to treat their pediatric patients with obesity, including additional FDA-approved drug therapies, particularly for children with severe obesity.
CONSIDERATION	*Unique ethical and practical issues come into play when studying any drug in children. However, when these issues can be resolved appropriately, children and adolescents should be included in clinical trials for obesity drugs once safety concerns have been addressed.*

FINDING	Important questions remain regarding what risk factors, in addition to obesity itself, warrant pharmacological intervention in pediatric patients. While >five percent weight loss is associated with a number of improved health metrics in adults, there is limited research that indicates the amount of weight loss required to improve risk factors and comorbidities in children and adolescents.
CONSIDERATION	*Pediatric patients with severe obesity could be considered candidates for drug therapy after the failure of more conservative therapies.*[38]
CONSIDERATION	*The government and/or research community should prioritize development of a registry of children and adolescents who have been treated with obesity drugs for an extended period of time to assess long-term outcomes and side effects.*

COMMENT | Treatment for children and adolescents with obesity should aim to reduce the patient to a healthy weight (below 85th percentile for age and gender) free of health-related complications associated with obesity. However, additional research is needed to determine how much weight loss leads to better health outcomes in children, in terms of feeling, functioning, and surviving. Furthermore, validated age-appropriate measures are needed to assess changes in feeling and functioning. Additional concerns exist around long-term drug therapy in children and adolescents as they develop, and whether the drugs will have consequences that may not be apparent for years. A national registry of children with severe obesity would be a useful tool for documenting the natural history risks of severe obesity against which benefits could be compared.

Conclusion

Scientific knowledge gained in the last two decades has identified some of the biologic mechanisms underlying obesity, as well as the environmental changes that predispose individuals to weight gain and make weight loss efforts so challenging. These research findings provide additional information with which to consider new treatment options for obesity, including pharmacotherapy.

The current FDA framework does not adequately categorize which types of patients with obesity could achieve benefits in feeling, function, and health risk. Nor does it adequately capture the many potential benefits of weight loss (short-term symptomatic, longer-term comorbidities, or effects on QoL) that may be improved through modest weight loss, aided by pharmacologic treatment.

A more comprehensive patient-centered approach in making risk-benefit determinations could help the FDA ensure that safe and effective obesity drugs are available to both adult and pediatric patient groups for whom the benefits of improved physical and mental health and QoL outweigh the risks associated with a particular drug.

While the considerations included in this report address a wide range of systemic problems confronting obesity drug understanding, development, approval, and appropriate usage, five critical points emerge which redefine how drugs developed to treat obesity should be viewed, developed, approved, and used:

1. Drugs under investigation for the clinical treatment of obesity should be reviewed as obesity treatments rather than weight loss agents.
2. Current clinical treatment options for obesity are limited, and obesity drugs may provide an additional intervention for helping individuals who do not respond, or inadequately respond, to other treatment interventions.
3. The benefit-risk evaluation of treatment with obesity drugs should extend beyond numerical weight loss to improvement in feeling and functioning. Drug development and review should more adequately capture and consider how obesity drugs affect how individuals feel and function on a daily basis.
4. Obesity is not a homogenous condition. The evaluation of the benefits and risks of pharmacologic intervention should reflect the different considerations within different categories based on feeling, functioning, and health impairments of obesity.
5. Use of obesity treatments should be limited to those for whom they are medically appropriate. Obesity drugs, like all drugs, come with side effects and risks. This requires responsible use and promotion and may require limiting access to obesity drugs to those individuals most likely to benefit due to their significant weight-related impairment in health, feeling, and functioning.

Appendix

FDA Guidance for Industry — Developing Products for Weight Management:[39]

Efficacy Endpoints

a. Primary efficacy endpoint

The efficacy of a weight-management product should be assessed by analyses of both mean and categorical changes in body weight.

- **Mean:** The difference in mean percent loss of baseline body weight in the active-product versus placebo-treated group
- **Categorical:** The proportion of subjects who lose at least five percent of baseline body weight in the active-product versus placebo-treated group

    a. Secondary efficacy endpoints

b. Secondary efficacy endpoint

Secondary efficacy endpoints should include, but are not limited to, changes in the following metabolic parameters:

- Blood pressure and pulse
- Lipoprotein lipids
- Fasting glucose and insulin
- HbA1c (in type 2 diabetics)
- Waist circumference

In clinical practice, waist circumference is used as an indirect measure of visceral fat content. When waist circumference increases, it is associated with elevated risk for metabolic abnormalities such as dyslipidemia and diabetes. Because the evaluation of investigational weight-management products routinely includes assessment of changes in patients' metabolic profiles, and in some cases may involve measurement of visceral fat content by CT or MRI, waist circumference should not serve as a surrogate for visceral fat content when measured in a clinical trial investigating the efficacy of a product for weight loss. Rather, it can be a means to confirm that reductions in waist circumference following treatment with a weight-management product are associated with expected improvements in metabolic parameters.

It is likely that a large portion of the subjects will be taking concomitant medications to treat weight-related comorbidities such as hypertension, type 2 diabetes, and dyslipidemia. Since weight loss is expected to improve these comorbidities, an important secondary efficacy endpoint should be the proportion of subjects treated with the weight-management product compared with placebo who have a meaningful dose-reduction or complete withdrawal of their concomitant medication. Algorithms that direct dose reduction or withdrawal of concomitant medications based on changes in levels of blood pressure, lipids, or glycaemia should be included in the study protocols.

Measures of quality of life from validated instruments can also be appropriate secondary endpoints

c. Efficacy benchmarks

In general, a product can be considered effective for weight-management if after one year of treatment either of the following occurs:

- The difference in mean weight loss between the active-product and placebo-treated groups is at least five percent and the difference is statistically significant
- The proportion of subjects who lose greater than or equal to five percent of baseline body weight in the active-product group is at least 35 percent, is approximately double the proportion in the placebo-treated group, and the difference between groups is statistically significant

Improvements in blood pressure, lipids, glycaemia, or other areas commensurate with the degree of weight lost are expected in patients treated with an effective weight-management product. Therefore, changes in common weight-related comorbidities should be factored into the efficacy assessment of investigational weight-management products.

EOSS: EDMONTON OBESITY STAGING SYSTEM - *Staging Tool*

STAGE 0

- **NO** sign of obesity-related risk factors
- **NO** physical symptoms
- **NO** psychological symptoms
- **NO** functional limitations

Case Example:

Physically active female with a BMI of 32 kg/m², no risk factors, no physical symptoms, no self-esteem issues, and no functional limitations.

Class I, Stage 0 Obesity

EOSS Score

WHO Obesity Classfication

STAGE 1

- Patient has obesity-related **SUBCLINICAL** risk factors (borderline hypertension, impaired fasting glucose, elevated liver enzymes, etc.)

- OR -

- **MILD** physical symptoms - patient currently not requiring medical treatment for comorbidities (dyspnea on moderate exertion, occasional aches/pains, fatigue, etc.)

- OR -

- **MILD** obesity-related psychological symptoms and/or mild impairment of well-being (quality of life not impacted)

Case Example:

38 year old female with a BMI of 59.2 kg/m², borderline hypertension, mild lower back pain, and knee pain. Patient does not require any medical intervention.

Class III, Stage 1 Obesity

WHO CLASSIFICATION OF WEIGHT STATUS (**BMI kg/m²**)

Obese Class I ..... 30 - 34.9
Obese Class II ..... 35 - 39.9
Obese Class III ..... ≥40

Stage 0 / Stage 1 Obesity

Patient ***does not meet clinical criteria for admission*** at this time.
Please refer to primary care for further preventative treatment options.

STAGE 2

- Patient has **ESTABLISHED** obesity-related comorbidities requiring medical intervention (HTN, Type 2 Diabetes, sleep apnea, PCOS, osteoarthritis, reflux disease) *- OR -*
- **MODERATE** obesity-related psychological symptoms (depression, eating disorders, anxiety disorder) *- OR -*
- **MODERATE** functional limitations in daily activities (quality of life is beginning to be impacted)

Case Example:

32 year old male with a BMI of 36 kg/m² who has primary hypertension and obstructive sleep apnea.

Class II, Stage 2 Obesity

STAGE 3

- Patient has **significant** obesity-related end-organ damage (myocardial infarction, heart failure, diabetic complications, incapacitating osteoarthritis) *- OR -*
- **SIGNIFICANT** obesity-related psychological symptoms (major depression, suicide ideation) *- OR -*
- **SIGNIFICANT** functional limitations (eg: unable to work or complete routine activities, reduced mobility)
- **SIGNIFICANT** impairment of well-being (quality of life is significantly impacted)

Case Example:

49 year old female with a BMI of 67 kg/m² diagnosed with sleep apnea, CV disease, GERD, and suffered from stroke. Patient's mobility is significantly limited due to osteoarthritis and gout.

Class III, Stage 3 Obesity

STAGE 4

- **SEVERE** (potential end stage) from obesity-related comorbidities *- OR -*
- **SEVERELY** disabling psychological symptoms *- OR -*
- **SEVERE** functional limitations

Case Example:

45 year old female with a BMI of 54 kg/m² who is in a wheel chair because of disabling arthritis, severe hyperpnea, and anxiety disorder.

Class III, Stage 4 Obesity

Alberta Health Services

UNIVERSITY OF ALBERTA

Sharma AM & Kushner RF, *Int J Obes* 2009

Figure 1: EOSS Staging System Staging Tool

Table 1: Consequences of Obesity and Measures of Improvement Impacted by Weight Loss [§]

"Long-Term" Outcomes	
1. Obesity-associated mortality	a. Obesity-associated mortality
2. Obesity-associated health conditions	a. Diabetes: Measures include diabetes rates (fasting blood sugar, 2-hour post-prandial blood sugar, hemoglobin A1c) or diabetes mortality rates b. Cardiovascular disease: Measures include cardiac events, myocardial infarction, stroke, and cardiovascular mortality c. Cancer: Measures include obesity-related cancer incidence, recurrence, and mortality rates d. Kidney disease: Measures include chronic kidney disease incidence and kidney dysfunction e. Fertility: Measures include fertility rates in patients with PCOS
"Intermediate Outcomes"/Risk Reduction	
3. Measures of intermediate endpoints for obesity associated health problems	a. Diabetes: Measures include changes in diabetes risk biomarkers (such as fasting blood sugar or fasting insulin) b. Cardiovascular disease: Measures include blood pressure, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, pulse, cardiorespiratory fitness, C-reactive protein, pro-inflammatory cytokines, and pro-thrombotic factors c. Non-alcoholic fatty liver disease: Measures include changes in liver enzymes, MRI fibrosis scores, or liver biopsy histology in patients with non-alcoholic fatty liver disease d. Polycystic ovarian syndrome: Measures include changes in ovulatory function and/or insulin sensitivity e. Chronic kidney disease: Measures include changes in kidney function f. Cardiorespiratory fitness: Measures include changes in VO2 Max and time to fatigue
"Immediate Outcomes"/Symptoms (On Following Page)	

[§] Note that these are common consequences of obesity, which are potential benefits of obesity treatment. However, it is not suggested that these need to be independently studied for approval of obesity treatments.

"Immediate Outcomes"/Symptoms (Cont'd From Previous Page)	
4. Measures of obesity-associated symptoms/QoL	a. Medication use: Measures include changes in medication use for diabetes, cardiovascular disease, hypertension, PCOS, osteoarthritis, acid reflux, etc. b. Sleep apnea: Measures include changes in symptoms of sleep apnea or clinical measures of sleep apnea (such as the apnea-hypopnea index) or reduction in continuous positive airway pressure(CPAP) use c. Urinary stress incontinence: Measures include changes in symptoms of urinary stress incontinence d. Polycystic ovarian syndrome: Measures include changes in ovulatory function, insulin sensitivity, and/or fertility in patients with PCOS e. Osteoarthritis: Measures include changes in symptoms of joint pain in patients with osteoarthritis f. Acid reflux: Measures include changes in symptoms g. Hypogonadism: Measures include changes in symptoms or testosterone levels
5. Measures of improvement in physical function	a. Mobility: Measures include changes in symptoms or improvement in 6-minute walk test b. Functional limitation: Measures include changes in symptoms
6. Measures of improvement in psychosocial and behavioral functioning	a. Overall and categorical quality of life: Measures include changes in symptoms b. Symptoms/level of depression: Measures include changes in symptoms, improvement in objective measures of depression c. General self-esteem: Measures include changes in symptoms (e.g. Rosenberg Self-Esteem Questionnaire) d. Body image (especially evaluative component measures): (e.g. Rosenberg Self-Esteem Questionnaire) changes in symptoms (e.g., Body esteem scale)

BMI in Children and Adolescents[40]

BMI in children is usually measured using a BMI-for-age scale, which allows pediatricians to account for age-related growth. After BMI is calculated for children and adolescents, the BMI number is plotted on BMI-for-age growth charts to obtain a percentile ranking. The percentile indicates the relative position of the child's BMI number among children of the same sex and age. The growth charts show the weight status categories used with children and teens (underweight, healthy weight, overweight, and obese).

BMI-for-age weight status categories and the corresponding percentiles are shown in the following table.

Weight Status Category	Percentile Range
Underweight	Less than the 5th percentile
Healthy weight	5th percentile to less than the 85th percentile
Overweight	85th to less than the 95th percentile
Obese**	Equal to or greater than the 95th percentile

** Children with a BMI significantly in excess of the 95th percentile are considered to have severe obesity, though as yet there is not a consensus definition of how to define severe obesity. Some clinical definitions of severe obesity in children used for research purposes thus far include, for example, BMI greater than 98th percentile, and BMI greater than 120% of the 95th percentile of weight-for-height.**

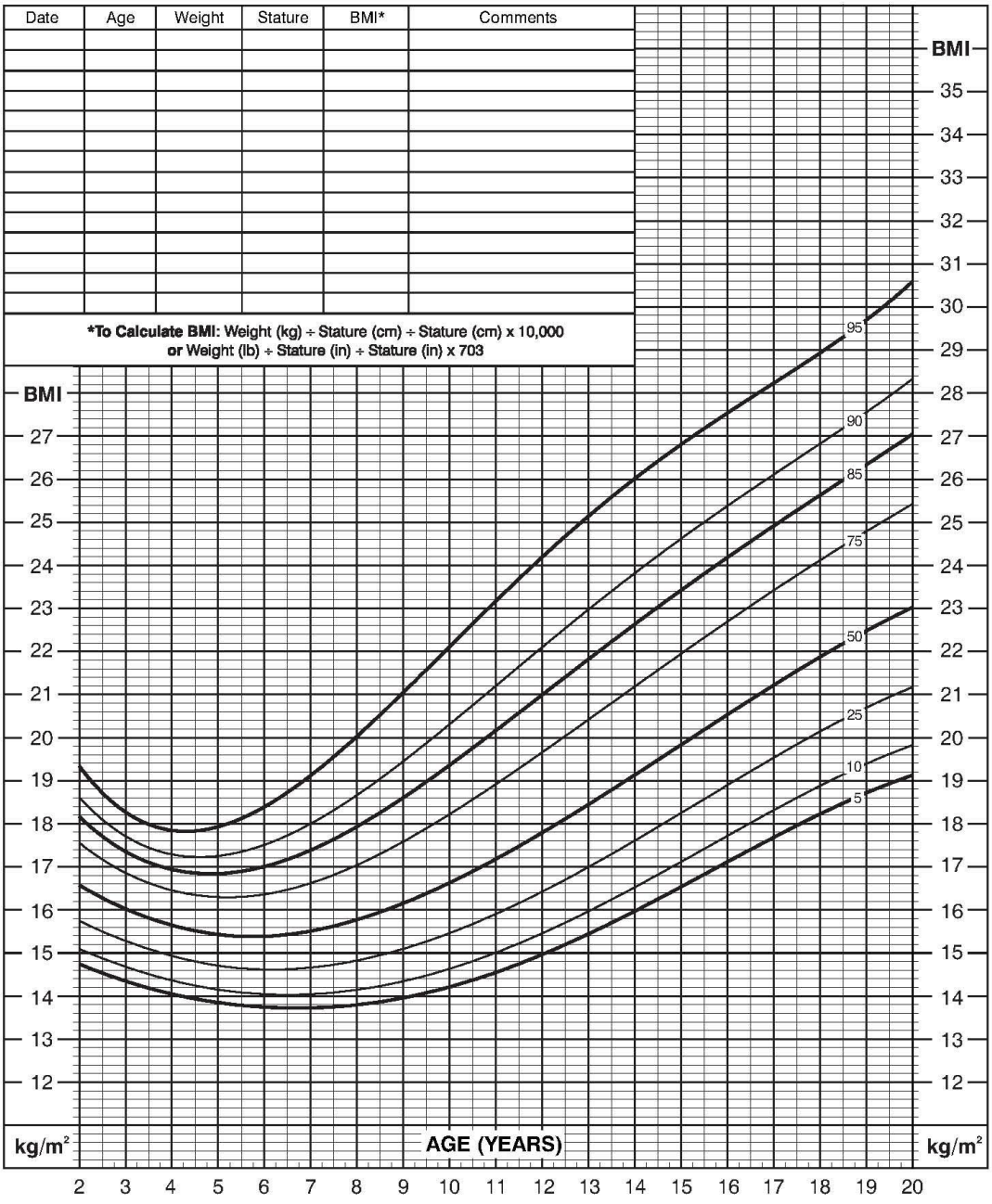
2 to 20 years: Boys
Body mass index-for-age percentiles

NAME _____

RECORD # _____

Date	Age	Weight	Stature	BMI*	Comments

***To Calculate BMI:** Weight (kg) ÷ Stature (cm) ÷ Stature (cm) x 10,000
or Weight (lb) ÷ Stature (in) ÷ Stature (in) x 703



Published May 30, 2000 (modified 10/16/00).
SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts

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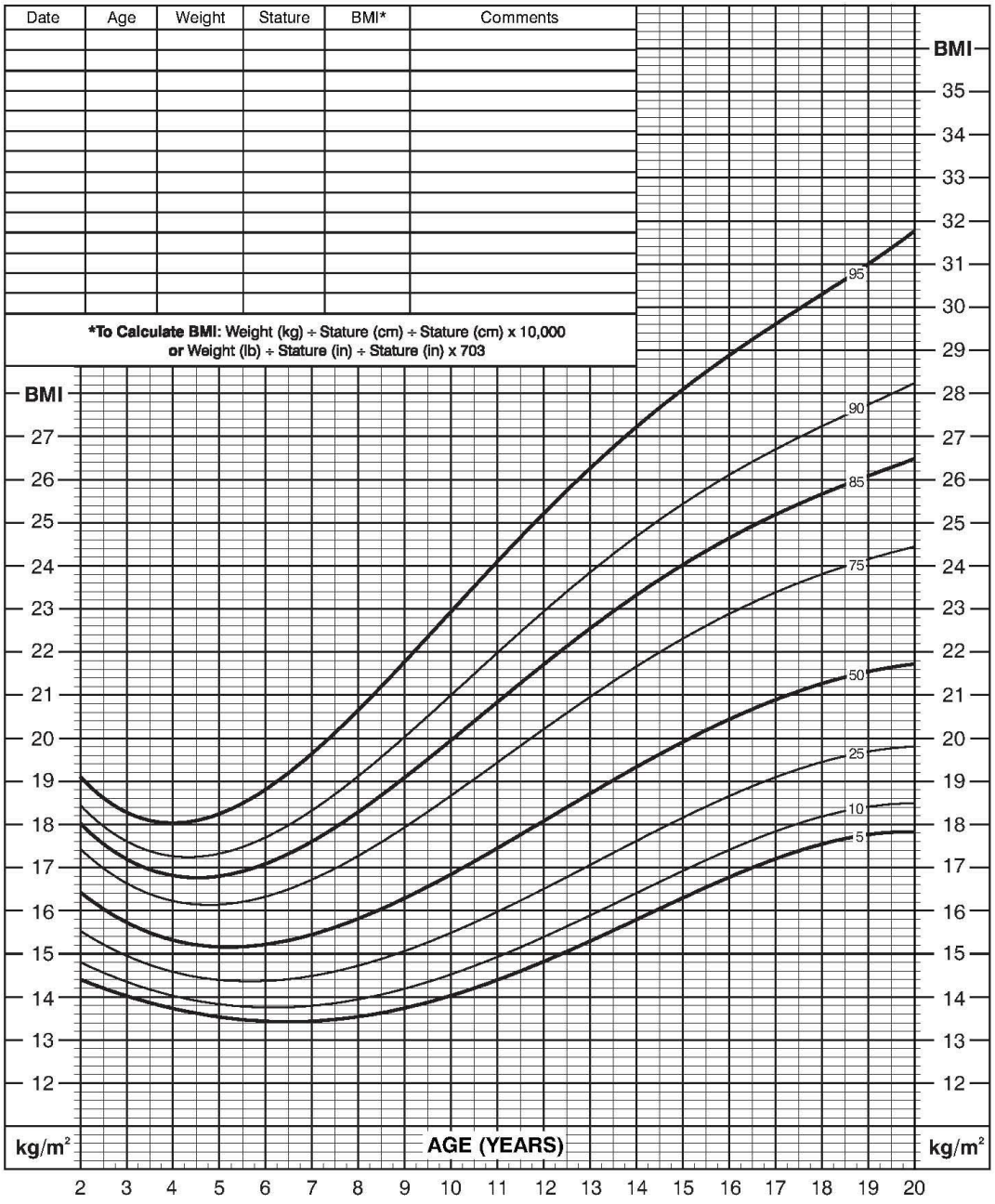
2 to 20 years: Girls
Body mass index-for-age percentiles

NAME _____

RECORD # _____

Date	Age	Weight	Stature	BMI*	Comments

***To Calculate BMI:** Weight (kg) ÷ Stature (cm) ÷ Stature (cm) x 10,000
or Weight (lb) ÷ Stature (in) ÷ Stature (in) x 703



Published May 30, 2000 (modified 10/16/00).
SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts

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