INAMED

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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Subject: Possible Barriers to the Availability of Medical Devices Intended to Treat or Diagnose Diseases and Conditions that Affect Children; Request for Comments [Docket No. 2004N-0254]

Ladies and Gentlemen:

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The purpose of this letter is to respond to FDA's request for comments concerning the above mentioned subject that was published in the *Federal Register* on June 21, 2004.

Inamed Corporation (Inamed) is a medical device manufacturer located in Santa Barbara, California, which manufactures (among other products) medical devices for the treatment of obesity, including the LAP-BAND® System. By applying FDA's existing final and draft guidances pertaining to the addition of indications for use of devices that have already been approved through the Premarket Approval (PMA) process for use on adults, Inamed believes that the FDA has an opportunity to expand the availability of medical devices such as the LAP-BAND® System that could offer significant clinical benefits to adolescents.

In response to the three questions posed by FDA below, Inamed offers the following comments that specifically address a serious epidemic in the United States: **severe obesity in children**.

1. **What are the unmet medical device needs in the pediatric population (neonates, infants, children, and adolescents)? Are they focused in certain medical specialties and/or pediatric subpopulations?**

   Inamed's Response:

   Among the unmet medical device needs in the pediatric population is the need for access to a safe, effective, less invasive, adjustable and reversible treatment for severe obesity. Such a treatment is already available to the adult population: Inamed's LAP-BAND® System, a laparoscopically placed, adjustable gastric band for the treatment of severe obesity.

Additional information regarding the extent and consequences of this unmet need and the potential benefits of access to the LAP-BAND® System follows:

The problem of obesity has reached epidemic proportions and is very costly.

- The United States and other countries are experiencing an epidemic of obesity affecting all age groups including children and adolescents.[1]
- Recent estimates suggest that over 15% of children and adolescents are obese (body mass index, BMI of $\geq 95^{th}$ percentile for age).[2]
- Obesity is the most frequent nutritional disease of childhood and adolescents.[3]
- Obesity ranks as a close second to smoking as a preventable cause of death and is well ahead of all other causes.[4]
- It is estimated that overweight and obesity account for 85% of cases of type 2 diabetes, 45% of cases of hypertension and 35% of cases of coronary artery disease.[5]
- A recent analysis of the extent of overweight among U.S. children concluded that not only have more children become overweight, the overweight children are becoming heavier.[6]

The societal costs of the obesity epidemic are very significant.

- It is estimated that obesity-related disease accounts for 5-12% of developed countries health costs, with type 2 diabetes alone accounting for 2-7%.[7,8,9]
- A conservative analysis concludes that annual obesity-related hospital costs <u>for adolescents</u> increased from $35 million during 1979-1981 to $127 million during 1977-1999, a three-fold increase.[10]
- For adults, the expenditures related to obesity in 2002 were estimated at $93 billion.[11]

Obesity has serious negative effects on children and adolescents.

Obesity in adolescents has a significant negative effect on current physical and psychological health and has major implications for future health with increased morbidity and mortality. Features of the metabolic syndrome, hypertension, dyslipidemia, impaired glucose tolerance and type 2 diabetes, are all reported in increased frequency in obese adolescents.[12,13,14,15]

- It is alarming that approximately 60% of overweight 5-10 year old children already have one biochemical or clinical cardiovascular risk factor, such as hyperlipidemia, elevated blood pressure, or increased insulin levels, and 25% have 2 or more.[16,17,18]
- The prevalence of the metabolic syndrome in adolescents in the U.S. is 4.2%, but for subjects below the 85th percentile, at the 85th–95th percentile and $>95^{th}$ percentile, the prevalence were 0.1%, 6.8% and 28.7% respectively.[19]

Other conditions, including nonalcoholic steatohepatitis,[20] obstructive sleep apnea,[21] and the polycystic ovary syndrome,[22] that are associated with the

metabolic syndrome and insulin resistance, are also being reported with increasing frequency in obese adolescents.

- Almost 50% of cases of cholecystitis in children and adolescents are associated with obesity.[23]
- Several cross-sectional and longitudinal studies have shown an increased prevalence of asthma in adolescents, especially girls.[24,25,26]
- Pseudotumor cerebri may be a cause of headaches in severely obese young women[27] and a number of orthopedic complications including Blount's disease[28] and slipped femoral ephysis[29] typically occur in overweight or obese children.

Obesity is associated with a greater mortality burden in younger people.[30] When estimated as years of life lost due to obesity, younger age and a higher body mass index (BMI) combine to reduce life expectancy. A white male in his 20's of BMI 36 is estimated to lose 4-years of life and with a BMI of 45 or greater, 13-years of life. At BMI 46 this represents a 22% reduction in remaining years of life.[31]

Obesity in adolescents is a very strong predictor of obesity as an adult.

- The risk is greatest for extreme overweight and when overweight is carried through late adolescence.[32,33]
- Once a child or adolescent reaches an overweight or obese percentile, spontaneous improvement is unlikely.[34]
- There is evidence that overweight and obesity during adolescence increases the risk of poor health in adult life independent of adult body mass index (BMI).[35,36]
- Among women but not men obese during adolescence, obesity has a variety of adverse psychosocial consequences. These include completion of fewer years of education, higher rates of poverty, and lower rates of marriage and household income.[37,38]

The psychosocial consequences of severe obesity in adolescents provide serious and pressing short-term comorbidity.

- The social burden of adolescent obesity may have lasting effects on body image, self-esteem and economic mobility especially in young women.[39] Obese adolescents suffer social bias, prejudice and discrimination as a result of their appearance.[40,41] In fact, the targeted discrimination of obese children starts early and is systematic.[3]
- These factors have been reported as the obese person's heaviest burden[42] and are experienced overwhelmingly by obese subjects.[40]
- This discrimination and bias has been recognized as coming from all sectors of the community including parents, teachers, medical and nursing professionals, and their fellow peers.[43,44]

The overall effect of physical and psychological impairment can be estimated, and compared with other conditions using health related quality of life measures.

- Schwimmer et al found, using a pediatric Quality of Life (QOL) inventory, that all domain scores were lower in obese children and adolescents when compared with non-obese controls.
- Obese children and adolescents were more likely to have impaired health-related QOL than healthy children and adolescents and were similar to children and adolescents diagnosed as having cancer.[45]

Non-surgical treatment has not been effective for severely obese adolescents.

The development of programs to reduce the incidence of pediatric obesity, including severe obesity, is needed and should be supported. However, there is a need to treat those who are already severely obese and are suffering from the consequences.

The conventional treatment of obesity in children and adolescents is the same as those in adults and include:

- a reduction in energy intake by dietary means,
- an increase in energy expenditure through an increase in both planned and lifestyle activity,
- an increase in energy expenditure through reduced sedentary behavior,
- modification of the behavioral habits associated with eating and activity, and
- involvement of the family in the process of change.[34]

Optimal and continuous application of a combination of dietary and drug therapy in association with increased exercise and behavioral modification can, at best, achieve and maintain a 5-10% loss of body weight in adults.[46,47,48,49,50] These methods may be adequate in cases of less severe obesity.

Use of these and more intensive therapies such as very low calorie diets[51] and pharmacotherapy[52,53] in adolescents has been very limited and have not produced significant and sustained weight loss. Of all the intensive therapeutic options for pediatric severe obesity, only bariatric surgery has produced significant sustained weight loss.[54]

Surgical treatment provides sustained and significant weight loss and improves or resolves obesity related conditions.

Remarkable and sustained changes in obesity related comorbidity have been reported following obesity surgery, including the gastric bypass and laparoscopic adjustable gastric banding. Over recent years the effect of significant weight loss following laparoscopic adjustable gastric banding surgery has been measured and documented[55,56,57,58,59,60,61,62,63,64,65,66,67,68] for a broad range of obesity related conditions including:

- type 2 diabetes,
- insulin resistance,
- dyslipidemia,

- hypertension,
- steatohepatitis,
- polycystic ovary syndrome,
- infertility,
- problems of pregnancy,
- sleep problems including obstructive sleep apnea,
- lung function,
- asthma,
- gastroesophageal reflux,
- health related quality of life,
- depression and
- body image.

Measures of quality of life and depression that are grossly impaired prior to surgery return to normal community values with weight loss.[69]

It is now recognized that type 2 diabetes, a serious condition strongly related to obesity, responds best to weight loss when treated early.

- Severe obesity, insulin resistance, and their metabolic and inflammatory consequences cause irreparable and progressive damage to insulin secreting pancreatic beta cells leading to the development of type 2 diabetes.
- Weight loss reverses this process, improving insulin sensitivity and allowing the reversible component of poor beta-cell function to recover.[64,65]
- If treated early, significant weight loss allows total remission of type 2 diabetes[64,70,71].
- This is also very powerful in preventing the development of type 2 diabetes in those at greatest risk.

Weight loss following obesity surgery has been shown to reduce mortality.

- Benotti et al following 5178 patients after restrictive gastric stapling procedures, found mortality in these patients to be similar to those of non-obese men and women.[72]
- MacDonald et al found a marked reduction in mortality rates in severely obese type 2 diabetic subjects surgically treated for obesity (1% risk of death/year) when compared with controls (4.5% risk/year).[73]
- Flum and Dellinger looked retrospectively at the mortality data in Washington State and found that subjects who were surgically treated had a reduced mortality when compared with non-surgically treated severely obese individuals. This benefit was more marked in the younger age group. In those under the age of 40 years the operated group had a mortality of 7.6% during the follow-up period compared to 15.9% in non-operated subjects.[74]
- A recent Canadian study by Christiou et al[75] reported a major reduction in mortality (89%) and reduced risk of developing obesity related comorbidity when compared with controls.

The gastric bypass procedures which were used in these studies have high peri-operative mortality (0.3-2%) when compared to adjustable gastric banding surgery (0.05%).[69,76] The benefit to risk ratio is strengthened greatly by the very low mortality associated with laparoscopic adjustable gastric banding surgery.

Weight loss surgery is successful in adolescents as well as adults, and has been recognized with recommendations from professional societies, but only the more invasive options are currently available for adolescents.

While there have been fewer reports published regarding bariatric surgery in an adolescent population, studies have reported positive benefits.

- Reports of both the gastric bypass and the LAP-BAND® System, including reports in the United States,[77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93] have concluded that they are safe and effective in producing sustained and significant weight loss and health improvements in both adolescents and adults.
- Most of the over 500 publications on the use of the LAP-BAND® System include patients 18-21 years of age, who are within the FDA's definition of adolescence.

Guidance for the surgical treatment of severe obesity in the pediatric population, including the LAP-BAND® System, has been provided:

- Focused primarily on concerns related to the gastric bypass but including laparoscopic adjustable gastric banding, recommendations were published in the July 2004 issue of *Pediatrics*.[94]
- In the same issue of Pediatrics, the American Society of Bariatric Surgeons supported and made recommendations in regards to obesity surgery in adolescents.[95]
- In August 2004, the Massachusetts Department of Public Health in collaboration with the Betsy Lehman Center for Patient Safety and Medical Error Reduction issued a report on patient safety issues in relation to obesity surgery in which obesity surgery was recognized as an appropriate treatment for severe obesity.[96]

Severely obese adolescents who are seeking obesity surgery are most frequently offered the gastric *bypass*. The FDA does not control the indications for use of the gastric bypass because it is a surgical procedure and the surgical staplers used in the procedure do not require FDA pre-market approval. On the other hand, use of the less invasive LAP-BAND® System on an adolescent is currently considered to be "off-label" use and would cause increased liability concerns. Therefore, the procedure that is commonly available to severely obese adolescents in the United States carries a greater risk of mortality, life-threatening complications and long-term nutritional deficiencies.[76,97,98]

The LAP-BAND® System offers important advantages for adolescents.

In 1993, Inamed introduced the LAP-BAND® Adjustable Gastric Banding (LAGB®) System, an adjustable gastric band, for the treatment of severe obesity, in Europe. In June 2001, after review of data from a 3-year multi-center clinical study in the United States and longer-term international data, the FDA approved the Premarket Approval Application (PMA) for this device for the treatment of severe obesity in adults.

- The LAP-BAND® System was granted "Expedited Review" by the FDA because it offered significant advantages, including reduced mortality, patient specific adjustment without further surgery, and reversibility. Following premarket approval, the FDA described it as a "significant medical device breakthrough."
- Globally, nearly 150,000 LAP-BAND® Systems have been used to provide significant and sustained weight loss.
- As noted above, this weight loss has been documented to be accompanied by the resolution or improvement of serious comorbidities of obesity (such as type 2 diabetes, obstructive sleep apnea, hypertension, dyslipidemia, gastroesophageal reflux, depression and others) and significant improvements in quality of life.
- There are no physical or anatomical reasons why the LAP-BAND® System would not function appropriately in adolescents, and patient management concerns can be addressed by labeling that specifies the need for assessment and support by appropriate and trained personnel.
- In its August 2004 Executive Report, The Massachusetts Department of Public Health, in collaboration with the Betsy Lehman Center for Patient Safety and Medical Error Reduction, recognized "[gastric bypass] as the procedure with the best long term data and [laparoscopic adjustable gastric banding] as the procedure with the least apparent risk to adolescent patients."[92]

Recently, the American Diabetes Association sent an "E-Mail Alert" to 75,000 health care practitioners, attaching a "Review of obesity and weight loss surgery," by Thomas L. O'Connell, MD, of Duke University Medical Center, which noted that…

> "[Obesity surgery] has proven to be a safe and effective means of losing significant and lasting weight and should be considered in those who are morbidly obese."
>
> "…The adjustable gastric banding procedure has recently gained recognition as a surgical option and offers some significant advantages. Unlike the vertical banded gastroplasty and RNYGB (Roux-en-y gastric bypass), the adjustable gastric band… involves no stapling of the stomach wall, no cutting or opening of the stomach, and no alteration of the gastrointestinal tract. Should it become medically necessary, the band can be removed and normal stomach

anatomy restored. Also, the degree of restriction created by the band can be adjusted by injecting or withdrawing saline through a port under the skin. This allows the size of the stoma (opening between the upper and lower stomach) to be changed to fit each patient's nutritional and weight loss needs."[99]

Factors of particular importance to adolescents include:

- The procedure has a much lower risk of death or life-threatening complications.
- There is no malabsorption with this procedure and thus there is a low risk of a significant nutritional deficiency that might affect growth or result in birth defects related to inadequate prenatal nutrition.
- The adjustability of the LAP-BAND® System offers flexibility in ongoing weight management. The band can be deflated for greater intake, as needed for example, during pregnancy or illness or remote travel.
- Should better therapy for obesity become available at some time in the future, if the patient could not adapt to the band, or for any other reason, the band can be removed laparoscopically with no significant change to the patient's original anatomy.

The availability of a minimally invasive, laparoscopic procedure that is safe, effective, easily adjustable, completely reversible, already available to the adult population and generally recognized as safer and less invasive than other procedures currently being used for adolescents should not be delayed.

2. **What are the possible barriers to the development of new pediatric devices? Are there regulatory hurdles? Clinical hindrances? Economic issues? Legal issues?**

Inamed's Response:

Barriers to the development of new pediatric devices include:

1) FDA's requirement for clinical studies in pediatric populations in order to obtain approval for commercial distribution. This includes FDA requests for *randomized controlled trials,* although no such trials may have been required for approval of the indications for adults. Randomized controlled trials with surgical devices are often difficult to design due to ethical and practical concerns. For example, randomizing adolescent patients to gastric bypass or the LAP-BAND® System would expose some adolescents to risks that may be considered excessive. Many surgeons believe that subjecting patients (whether young *or* adult) to gastric bypass surgery when the use of the LAP-BAND® System is a safer alternative would be unethical in an investigational study. Even non-randomized prospective clinical studies significantly delay access and impose high costs that manufacturers may be unable or unwilling to incur. For example, the manufacturer may be required

to pay all costs, including the surgical procedures, in order to obtain adequate enrollment.

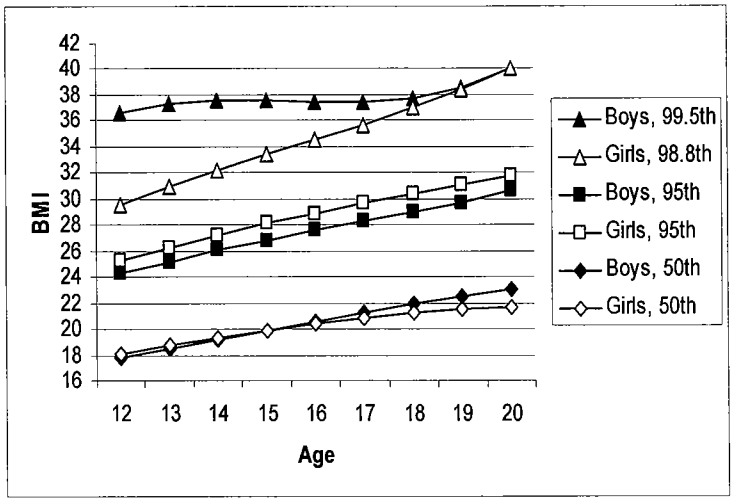
2) Potential FDA reluctance to apply existing draft guidance regarding the application of medical devices to pediatric populations (Premarket Assessment of Pediatric Medical Devices: July 24, 2003). This guidance requires an analysis of the various issues of concern in applying a device to a pediatric population but acknowledges that clinical studies *should not be necessary* if there is no substantial change to the device or its application.

3) Potential FDA reluctance to accept literature evidence and population analysis in lieu of prospective clinical studies, although an FDA final guidance (Guidance to Industry Supplements to Approved Applications for Class III Medical Devices: Use of Published Literature, Use of Previously Submitted Materials, and Priority Review; Final; May 20, 1998) exists.

4) Lack of stratification of pediatric populations in terms of regulatory requirements. For example, the risk of using an adult device in a 16 year-old adolescent is very different from using that same device in a 6 year-old child or a 6 month-old infant.

5) Potential FDA emphasis on possible risks, rather than known benefits, of technologies already applied to adults, and on restricting access rather than working with manufacturers to provide safe but earlier access. For the LAP-BAND® System, for example, surgeon and site qualifications, training, and the appropriate screening and management of adolescent patients by qualified personnel could be specified in the labeling.

6) The small market size (and thus smaller financial opportunity) associated with pediatric indications compared to indications for adults presents an economic challenge. As can be seen in the growth chart below, severely obese adolescents comprise only a small fraction of the pediatric population, and also only a small fraction of the total population of severely obese patients. Investment by a manufacturer in the introduction of products for a small market that also is associated with increased liability concerns and additional marketing, training and sales costs is made more difficult when regulatory barriers are expensive and difficult to overcome.



7) The cost associated with manufacturing and stocking additional versions of a product can be significant. Although this is not anticipated with the LAP-BAND® System, it is an issue that increases the costs associated with other types of pediatric devices. The shorter life cycles and lower barriers to entry of medical devices (when compared to pharmaceuticals) result in more frequent changes to products. Multiple sizes of products increase the costs of these changes. In addition, the effects of the change must be assessed for all populations and may require regulatory activity and resources.

8) Another barrier is the significant liability risk associated with pediatric use of medical devices for health care practitioners, institutions and industry.

3. **What could FDA do to facilitate the development of devices intended for the pediatric population? Are there changes to the law, regulation, or premarket process that would encourage clinical investigators, sponsors, and manufacturers to pursue clinical trials and/or marketing of pediatric devices?**

Inamed's Response:

To encourage manufacturers to pursue marketing of devices for the pediatric population, the FDA could:

1) Encourage submissions for adolescent indications using PMAs based on data obtained in clinical studies on adult populations plus a rationale using existing pediatric guidance, combined with post-market studies, if appropriate.

2) Complete and apply reasonable guidances for pediatric applications of adult medical devices, which would emphasize access under appropriate controls.

3) Accept design analysis, literature and non-clinical evidence in lieu of prospective clinical studies for products already approved for use in adults, for example as described in the final FDA guidance on the use of literature, noted above.

4) Stratify regulatory requirements for pediatric populations to facilitate expansion of availability of adult devices to older groups who are more similar physiologically to young adults than to young children. Adolescence has been defined as ages 12-21, and this includes patients from 18 to 21 for whom the LAP-BAND® System and other "adult" devices are already commercially available. It appears reasonable that there should be fewer barriers to expanding the use of adult devices to teenagers than to toddlers.

5) Require additional clinical studies on devices that have gone through the Premarket Approval process only when significant uncertainties exist and pose serious risks that outweigh the benefits of access to such devices.

6) When issues that affect risk can be addressed through labeling modifications (i.e., user qualifications, indications and contraindications, training, warnings), this method should be used. It will facilitate earlier access to important technology.

7) Maintain existing policy of no user fees for applications for pediatric indications for adult medical devices.

8) Reduce user fees applied to all medical device submissions, which discourage and slow implementation of improvements and which decrease manufacturers' resources for development and introduction of pediatric devices.

9) Reduce post-approval clinical risks by working with manufacturers on labeling which restricts use to qualified and trained physicians at centers having appropriate staff, facilities and programs. This has been carried out successfully with the adult indication for the LAP-BAND® System, for example.

10) Reduce the liability risk associated with the use of medical devices in the pediatric population through legislation.

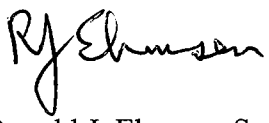
11) Apply "expedited review" to pediatric regulatory applications or otherwise shorten the review time, particularly for applications aimed at expanding indications for use of devices already approved for use in adults.

These rather detailed comments have been provided to illustrate, by example, an urgent, unmet need in a pediatric population and to suggest ways of satisfying that need. Not all the support and rationale for expanding access of the LAP-BAND® System to adolescents have been presented.

To summarize:

- Although obesity has reached epidemic proportions in the pediatric population and has serious and long-lasting negative consequences for health and quality of life, the current non-surgical weight loss treatments, at the very best, achieve a sustained weight loss of 10% of body weight, which is unlikely to substantially influence the medical, physical and psychological problems of severely obese adolescents.
- Obesity surgery is the only effective therapy in this population, whether adult or adolescent.
- Because of the recognized advantages of the LAP-BAND® System, including safety, minimally invasive placement, adjustability and reversibility, Inamed believes that this device should be available for use on appropriate severely obese adolescents in qualified centers with minimal delay.
- Inamed suggests that stratification of the pediatric populations, recognition of the similarities between adolescent and adults, application of existing FDA guidances, and greater focus on labeling to optimize results during commercial distribution will expedite the availability of beneficial therapies for adolescents.

Respectfully,



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