GUIDANCE DOCUMENT FOR INDUSTRY AND CDRH STAFF FOR THE PREPARATION OF INVESTIGATIONAL DEVICE EXEMPTIONS AND PREMARKET APPROVAL APPLICATIONS FOR BONE GROWTH STIMULATOR DEVICES

Draft Document

This guidance document is being distributed for comment purposes only.

Division of General and Restorative Devices
Office of Device Evaluation

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Dockets Management Branch
Division of Management Systems and Policy
Office of Human Resources and Management Services
Food and Drug Administration
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PREFACE

The development of a guidance document for bone growth stimulator (BGS) devices is based on the evaluation of numerous such devices by the Center for Devices and Radiological Health (CDRH), Food and Drug Administration (FDA), and the recognition of certain criteria necessary to conduct these evaluations. The purpose of this document is to suggest to the device manufacturer or investigation sponsor important preclinical and clinical information which should be presented in Investigational Device Exemptions (IDE) and Premarket Approval (PMA) applications in order to provide reasonable assurance of the safety and effectiveness of these devices for their intended uses. The suggestions and recommendations written in this document reflect methodologies which CDRH has determined to be acceptable and which, if followed, will help to produce well designed and scientifically valid IDE and PMA applications. In this context, several points should be remembered:

1. The guidance document suggests some important evaluation criteria, test procedures, and clinical end points. If the same objectives can be achieved by other means, the investigator should not refrain from exploring alternative approaches.

2. The guidance document should be viewed as a "living" document. As science changes and scientific techniques are improved, CDRH will periodically revise the document. Nonetheless, it should be remembered that the basic objectives may remain the same.

3. This guidance document represents the agency's current thinking on BGS devices. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

Updating of the guidance document was initiated by the Division of General and Restorative Devices (DGRD) of the Office of Device Evaluation (ODE). The updated guidance will undergo review by representatives of DGRD, the Orthopedic and Rehabilitation Devices (ORD) Advisory Panel, and other industry and non-industry representatives. Comments and recommendations generated by these reviews will be used to draft a document, and will be presented for discussion during an open public session of the ORD Panel meeting.

All FDA publications referred to in this guidance document can be obtained by contacting the Division of Small Manufacturers Assistance (DSMA) at 800-638-2041 (toll free) or 301-443-6597. Some publications can be obtained via DSMA's Internet site at www.fda.gov/cdrh/dsmamain.html. Additional questions concerning this document should be directed to DGRD at (301) 594-2036.

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INTRODUCTION

SCOPE

This guidance document is applicable to all bone growth stimulators (BGS). For the purpose of this document, the term "bone growth stimulator" is intended to describe not only those devices used to initiate bone growth (e.g., for fracture healing), but also to describe devices used to treat other bone conditions such as osteoarthritis, avascular necrosis, osteoporosis, spinal fusion, etc.

OBJECTIVES

In discussions and correspondence with sponsors of BGS devices of various modalities and other interested parties, the Center for Devices and Radiological Health (CDRH) has been asked to address several important issues relating to the preparation of Investigational Device Exemptions (IDE) and Premarket Approval (PMA) Applications. This document responds to these issues and provides additional guidance detailing the Office of Device Evaluation's (ODE) present perspective on issues related to these devices.

Based upon the potential for serious risk associated with chronic exposure to electrical, electromagnetic, and ultrasound energies at the cellular and molecular levels, the Food and Drug Administration (FDA) regards all bone growth stimulators as significant risk devices. The device manufacturer or investigation sponsor (hereafter referred to as the sponsor) must have an approved IDE before initiating a clinical trial with a BGS device. Institutional review board (IRB) approval alone is not sufficient to commence a clinical trial on human subjects involving a new BGS device. Prior to marketing these devices, an approved PMA is required.

The primary objective of this guidance document is to assist sponsors in the preparation of IDE and PMA applications for the purpose of initiating and reporting the results of clinical studies of BGS devices intended for the treatment of a variety of bone conditions including, but not limited to, fresh, delayed union, and non-union fractures. For the purposes of this document, a non-union is defined as a fracture that is acquired secondary to trauma, excluding vertebrae and all flat bones. For the purposes of the IDE clinical study protocol, and to reduce the potential for a heterogeneous population with respect to the age and type of fracture, the decision that a non-union has been established should not be made until a minimum of nine months has elapsed since the injury, and the fracture site has shown no visibly progressive signs of healing, i.e., no change in the fracture callus, for the final three months (i.e., six months to be considered a non-union plus three additional months to verify (for study purposes) that the non-union is established). To avoid confounding the results of the investigation, CDRH strongly recommends that there be no surgical or therapeutic intervention at the fracture-site during the three months immediately prior to device use.

This time-based definition of non-union may not be readily applicable to other fracture types and bones. In an IDE application for the investigation of the use of a BGS device to treat other bone conditions, e.g., osteoarthritis, avascular necrosis, osteoporosis or spinal fusion, it is the responsibility of the sponsor to propose the specific definitions of the medical indication. For example, in the case of spinal fusion, consideration should be given to the differences in rate of healing between the spine and bones of the appendicular skeleton in specifying the time to a healed fracture.

This guidance document provides a framework to assist in developing clinical studies and generating scientific evidence which will provide reasonable assurance of the safety and effectiveness of the BGS device for its intended use. The general principles regarding the information to be contained in an IDE or a PMA submission applies equally to all modalities of BGS devices.

This guidance document serves as a supplement to other FDA publications on IDE and PMA applications and should not be construed as a replacement for these documents. The Division of General and Restorative Devices (DGRD) may be consulted prior to the initiation of any tests or during the preparation of applications if, after reading all of the relevant publications, questions remain concerning specific requirements for a BGS device application. Although use of this document to prepare preclinical and clinical protocols will not ensure IDE or PMA approval, following this guidance will reduce unnecessary work on the part of device manufacturers/sponsors, and will allow for a more efficient review by FDA.

REGULATORY AUTHORITY

FDA regulations relevant to this document can be found in the Code of Federal Regulations, Title 21 (21 CFR):

1. General Information
   - Determination of Safety and Effectiveness (defines valid scientific evidence) (21 CFR 860.7)
   - Environmental Impact Considerations (21 CFR 25)

2. Investigational Devices
   - Protection of Human Subjects; Informed Consent (21 CFR 50)
   - Standards for Institutional Review Boards for Clinical Investigations (21 CFR 56)
   - Good Laboratory Practice (GLP) Regulations (21 CFR 58)
   - Investigational Device Exemptions (21 CFR 812)

3. Premarket Approval Devices
   - Medical Device Reporting (21 CFR 803)
   - Premarket Approval of Medical Devices (21 CFR 814)
   - Quality System Regulation / Current Good Manufacturing Practice (CGMP) Requirements for Medical Devices: General (21 CFR 820)

ABBREVIATIONS USED IN THE DOCUMENT

Bone growth stimulator (BGS)
Center for Devices and Radiological Health (CDRH)
Division of Life Sciences (DLS)
Division of Physical Sciences (DPS)
Division of General and Restorative Devices (DGRD)
Division of Small Manufacturers Assistance (DSMA)
Food and Drug Administration (FDA)
Health Industry Manufacturers Association (HIMA)
Institutional Review Board (IRB)
International Standards Organization (ISO)
Investigational Device Exemption (IDE)
Office of Device Evaluation (ODE)
Office of Science and Technology (OST)
Orthopedic and Rehabilitation Devices Advisory Panel (ORD Panel)
Premarket Approval Application (PMA)
Pulsed electromagnetic field (PEMF)

CONTENTS OF THE IDE APPLICATION

Sponsors of clinical investigations must carefully consider how to adequately demonstrate the safety and effectiveness of their specific device(s). Studies must be designed to ensure that the data will provide valid scientific evidence (as defined in 21 CFR 860.7) which will satisfactorily answer all appropriate questions and which will form a sound basis to support the medical claim(s) being made.

Sponsors should address both the safety and effectiveness of their devices in a PMA application. These are relative terms which ultimately should be considered together to show that the probable benefits to health from the use of the device outweigh the probable risk. Normally, these points should be addressed with data collected during a clinical trial using the particular device. For a BGS device, this clinical trial should be conducted under an approved IDE. In addition, relevant *in vitro* and *in vivo* studies should be included in both the IDE and PMA applications to support the safety of the device. Furthermore, demonstration of efficacy in a relevant animal model may be needed prior to the clinical trial, depending on the clinical indication being studied.

This document provides guidance for the preparation of four sections of the IDE application for a BGS device: manufacturing, device description, preclinical data, and clinical data; as well as additional points to consider for preparation of the PMA application. Sponsors should consider both the general and specific recommendations contained in each section in order to adequately document any claims for their specific devices. After reviewing this information, any remaining questions can be addressed by consulting DGRD.

An IDE application should include, but not be limited to, the following information.

MANUFACTURING

Pursuant to 21 CFR 812.20(a)(3), the sponsor should provide a description of the methods, facilities and controls used for the manufacture, processing, packaging, storage and, where appropriate, installation of the device, in sufficient detail so that a person generally familiar with good manufacturing practices can make a knowledgeable judgment about the quality control used in the manufacture of the device. This information should be provided for both the device and any accessory components used with the device, such as, monitoring and recharging units. Pass/fail criteria for the critical steps in the manufacturing process of the device should be included. Sponsors of invasive devices should specify the sterilization method(s) used, all parameters of the sterilization cycle, sterilization level (e.g., 10^{-6}), and information concerning the validation of the sterilization process. Additionally, in some cases when a device or one of its components is intended to be implanted, information on pyrogen and/or endotoxin content should be submitted.

DEVICE DESCRIPTION

The sponsor should provide sufficiently detailed information to characterize the device's components, output, measurement procedures, and instrumentation used in obtaining these measurements. A physical description of the device, components, accessories, controls, displays, connections, etc. as well as a complete description of the output signal should be provided. Detailed procedures used for prescribing applicator assemblies (e.g., a specific applicator for a specific anatomical location or limb size) and any adjustments of the therapeutic signal parameters needed to meet individual patient treatment requirements should be provided. At a minimum, the following descriptive information should be included.

A. Physical Description

Provide a complete physical description of all device components and accessories, and describe the method of connection between components and accessories. Indicate the dimensions, weights, and material

composition of each component, and include appropriately labeled engineering drawings and/or photographs.

B. User Interface

Describe all user and physician controls and displays, and all indicators used to convey operational status and patient compliance information. Describe the specific intended anatomical location and orientation of each unique transducer/applicator relative to the treatment site. Describe the method by which the applicator and signal generator are attached to the patient. Describe all "human factors" considerations employed in the device design.

C. Power Source

Provide a complete description of the power source. For battery-powered devices, describe the number, size, and chemical type (e.g., alkaline, lithium, Ni-Cad), and describe the battery longevity relative to the treatment duration. For rechargeable batteries, describe the recharging equipment, recharging methods, and time required to fully recharge depleted batteries. If recharging is possible during device use, describe the methods used to isolate the patient from the AC power source, and provide the results of leakage current testing.

D. Electrical Characteristics

Provide oscilloscope tracings of the therapeutic signal generator output waveform (with appropriate applicator connected). If the generator is capable of providing more than one waveform type and/or can be used with applicators of more than one type or size, an oscilloscope tracing of each waveform/applicator combination should be provided. In addition to quantitatively identifying all salient features of the output waveform, specify the horizontal and vertical oscilloscope gain settings. As a supplement to the oscilloscope tracings, provide a sketch of the output waveform with all stimulation parameters and temporal characteristics clearly labeled. In conjunction with this sketch, provide a table which summarizes the output specifications, with each specification listed as an acceptable range or as a single value ± tolerance.

E. Other

In addition to the information requested above, the following information should be submitted, to the extent that it applies to the specific device technology employed. Furthermore, sponsors of devices having unique characteristics or using technologies other than those categorized below are advised to provide sufficient additional detailed information considered necessary to adequately describe the device.

1. PEMF and Magnetic Field Devices

Clearly define the treatment target tissue and the specific location of the treatment target area. Identify the anatomical structures which define the target area and describe the location of these structures relative to the magnetic field and relative to each unique transducer orientation. In addition, provide the acceptable ranges of therapeutic signal specifications for the signal parameters, including the magnetic field (B) and the time rate of change of the magnetic field (dB/dt).

Provide a detailed description of the magnetic fields and of dB/dt throughout the region over which the device's therapeutic signal is targeted. For each transducer and for each transducer orientation or configuration, provide the following:

a. Provide oscilloscope waveforms of the magnetic fields and of the time rate of change of the dynamic magnetic field (i.e., dB/dt) corresponding to one complete cycle of the output signal. The measurements should be made with the magnetic field probe (e.g., detector coil) located in a region representative of the center of the treatment target area.

b. Provide a complete mapping (i.e., throughout the entire treatment target area) which characterizes the magnetic field, and dB/dt, averaged over the duration of the primary pulse. Specifically, for each transducer and for each transducer position, present three-dimensional mapping data which show the measured values at each location. A sufficient number of locations should be used to adequately describe the fields throughout the entire treatment target area. Spatial intervals of no greater than 2 cm are recommended. If the transducer is located in proximity to tissues which potentially may be adversely affected by the treatment signal, additional characterization of the signal levels in these regions may be necessary.

c. Discuss the methodologies used to obtain all requested waveforms and field maps. Include a complete description of all instrumentation, calibration procedures, and conversion factors used in the acquisition and presentation of data, and specify the physical dimensions, number of turns, winding arrangement and spatial resolution of the detector coil.

d. Spectral analyses should be provided to characterize the frequency content of the signal delivered through each transducer. Indicate the gain setting and bandwidth for each plot and describe the methods and instrumentation used to obtain the data.

e. Describe the number of turns and the winding arrangement of each transmitting coil, and provide a description of the electrical characteristics of the transmitting coil including the resistance, inductance and capacitance (where applicable).

2. Electrical Devices

Implantable

In addition to the physical description noted above, provide a detailed description of all implanted materials, the duration of implantation of each component, and a detailed biocompatibility report. Please refer to the Preclinical Data section of this guidance for additional considerations.

a. Generator

Describe the dimensions and materials of the generator case, and the method of attaching the generator to the patient and to the leads. Describe the method of sealing the generator electronics from the patient, and provide results of hermeticity testing. Provide labeled oscilloscope tracings and a detailed description of the generator output signal. Describe the nature of the signal source (e.g., regulated current or regulated voltage), test results documenting the longevity of the battery, and the method of programming and monitoring the generator output signal.

b. Leads and Electrodes

Describe the dimensions, materials, and configuration of the leads and electrodes, and clearly indicate the method of attaching the leads and electrodes to the patient. Identify the anode(s) and cathode(s) and describe the surface area, current density, charge density, and power density for each. Provide an equivalent circuit diagram for the generator and all leads, noting all impedance values. Indicate the estimated current density and/or electric field strength at the treatment site. Describe the placement of the anode(s) and cathode(s) relative to each other, relative to the treatment site, and relative to surrounding structures and excitable tissues (e.g., heart, peripheral nerves, spinal nerves, etc.).

Capacitively-Coupled

a. Provide a complete description of the output signal including the following:

(1) Oscilloscope tracings of the output waveform (with appropriate applicator connected) under loads of 500Ω, 2kΩ, and 10 kΩ should be presented as voltage versus time. If the generator is capable of producing more than one waveform type and/or can be used with applicators of more than one type or size, an oscilloscope tracing of each waveform combination should be submitted. In addition to quantitatively identifying all salient features of the voltage and time variables, the horizontal and vertical oscilloscope gain settings should be specified. The procedure for making the waveform measurements should be described;

(2) Maximum output current;

(3) Maximum and RMS output voltage;

(4) Specify whether the signal is constant current or constant voltage;

(5) Waveform (e.g., biphasic or monophasic) and frequency;

(6) Current density at the electrode/skin interface (using the area of the smallest electrode available for use with the device);

(7) Power density at the electrode/skin interface (using the area of the smallest electrode available for use with the device);

(8) Charge per pulse and charge density at the electrode/skin interface (using the area of the smallest electrode available for use with the device); and

(9) Estimated current density at the treatment target site.

b. Describe the dimensions, materials, and configurations of the leads and electrodes, and clearly indicate the method of attaching the leads and electrodes to the patient. Describe the placement of the electrodes relative to each other, relative to the treatment site, and relative to the surrounding structures and excitable tissues (e.g., heart, peripheral nerves, spinal nerves, etc.).

3. Ultrasound Devices

a. Provide the following acoustic output parameters including error uncertainties and the procedures used in obtaining measurements. (Refer to FDA guide 85-8240, "A Practitioner's Guide to The Ultrasonic Therapy Equipment Standard," available from DSMA, for further explanation of these parameters):

- ultrasound frequency
- pulse width
- pulse repetition rate
- beam non-uniformity ratio (BNR)
- effective radiating area (ERA)
- duty cycle [ratio of pulse duration to total period]
- temporal average power (Watts, W)

- temporal maximum power (W) [average power during a pulse/burst]
- instantaneous peak power (W)
- maximum effective intensity (W/cm^2) [temporal max power divided by the ERA]
- spatial-average-temporal average (SATA) intensity (W/cm^2) [temporal average power divided by the ERA]
- effective intensity (W/cm^2) [total ultrasonic power divided by the ERA].

b. Provide an acoustic beam profile (i.e., hydrophone measurements) describing the near and far fields.

c. Provide a complete description of the applicator including, but not limited to the following:

- size
- type (i.e., collimating, diverging, focusing. If focusing, include focal length and focal area)
- crystal material
- describe the placement of the applicator relative to the treatment site and relative to the surrounding structures and excitable tissues (e.g., heart, peripheral nerves, spinal nerves, etc.).

d. Provide a description of the coupling agent or gel to be used with the device.

e. Describe the device calibration and a maintenance schedule for recalibration.

f. Verify that the device has an acoustic power indicator that is accurate within ± 20% and a visual indicator that energy is being applied to the applicator.

g. Verify if the device complies with 21 CFR 1050.10 - Performance Standards for Ultrasonic Therapy Products.

F. Software/Firmware

If the device includes a microprocessor component, adequate detail should be provided to enable a person generally familiar with software development procedures to make a knowledgeable judgment concerning: 1) the degree to which the software meets the functional requirements, 2) the validation and verification performed throughout the software development life cycle, 3) the hazard analyses performed to identify potentially harmful conditions, and 4) the testing performed to ensure that the software functions as desired. For more information on software documentation, consult the draft *Reviewer Guidance for Computer Controlled Medical Devices Undergoing 510(k) Review*, dated August 29, 1991, and the draft document *ODE Guidance for the Control of Premarket Submissions for Medical Devices Containing Software*, issued for comment in September, 1996.

G. Electromagnetic Compatibility

FDA has become increasingly concerned about medical device malfunction due to electromagnetic interference (EMI). Maintaining reasonable immunity to electromagnetic energy and controlling excessive electromagnetic emissions are essential to the safety and effectiveness of medical devices.

Accordingly, provide a detailed electromagnetic compatibility (EMC) test plan which summarizes all planned EMC testing procedures. In addition, and where applicable, the following information should be collected prior to or during the IDE stage and submitted in the PMA application to demonstrate that the device operates safely and effectively in its intended use environment:

a. Provide results of electromagnetic immunity testing to demonstrate that the device performs as intended when subjected to radiated and conducted electromagnetic energy, magnetic fields, electrostatic discharge (ESD), transient bursts, and surges; and

b. Provide results of radiated and conducted electromagnetic emissions and magnetic emissions testing, to demonstrate that nearby devices would not be subjected to excessive electromagnetic energy from the device, which could adversely affect the performance of those nearby devices.

Provide a copy of the EMC test report, including an indication of the standard(s) to which the device was tested, the rationale for applying the chosen standard(s), test procedures and protocols, pass/fail criteria, test results, and a summary. Justify any omission or lack of testing with supporting scientific rationale and a hazard analysis. It is recommended that testing be performed in accordance with IEC 601-1-2 (*Electromagnetic Compatibility for Medical Electrical Equipment: Requirements and Tests*) to demonstrate the device's electromagnetic compatibility in its intended use environment. Furthermore, it is recommended that additional test data be provided in accordance with appropriate standard(s) to document the device's magnetic field emissions and its immunity.

PRECLINICAL DATA

The purpose of preclinical testing is to ensure that patients are not placed at undue risk in a clinical trial and to provide a reasonable probability that the device intended for treating a specific condition will demonstrate efficacy. To address these areas, options available to the sponsor include animal testing, previously published scientific literature, and development of theoretical rationales based on current knowledge. A combination of these approaches will prove to be the best choice in most situations.

The specific requirements for preclinical testing are influenced by the nature of the device and the specific clinical indication being studied. For example, implantable devices will require more extensive biological testing as compared to non-implantable devices. Also, in cases where metallic hardware is used, additional testing may be required to provide assurance that the hardware materials do not interfere with the device's therapeutic signal. Similarly, testing for effects on nervous tissue may be required for spinal fusion indications but may not be necessary for a study of tibial fracture non-union. In addition, testing performed to determine the cellular effects of the stimulation may vary depending upon the safety concerns associated with the specific nature of the stimulation. Consultation should be made at an early stage with DGRD to determine what preclinical tests are appropriate.

A comprehensive summary of all preclinical testing should be included in addition to specific detailed test descriptions. For each test, the sponsor should specify the device components being tested, the test procedures (including equipment, protocol, and measurement techniques), and test parameters. The test results should be discussed in terms of the expected *in vivo* and clinical performance of the device.

In general, all preclinical test data should be provided before an IDE can be approved for the initiation of a clinical trial. The sponsor should state whether or not all preclinical safety tests were performed in compliance with Good Laboratory Practices (GLP), 21 CFR Part 58. The GLP regulations are limited to safety studies; that is, those which can be used to predict adverse effects of, and to establish safe use characteristics for, a regulated product. Functionality studies are excluded. However, all nonclinical tests should be conducted according to good scientific practice. In terms of actual preclinical testing of a BGS device, the following items should be carefully considered by the sponsor in developing data for incorporation in an IDE:

A. Safety

Different safety concerns have been identified in the literature for each of the modalities for BGS devices, i.e., PEMF, ultrasound, DC, etc. Therefore, safety testing should be performed to address the safety issues related to the specific modality involved. For example, the potential for thermal and non-thermal effects of ultrasound waves should be investigated for BGS devices using this modality. In general, the information obtained from such studies should include histology and gross morphology of the treated bone.

1. In order to determine the toxicity testing recommended for a particular BGS device, the sponsor should refer to ISO 10993 and ODE guidance G95-1 (see Bibliography). The degree of testing depends on (1) the nature of the contact between the device and the body (e.g., external, externally communicating, or internal contact), (2) the duration of this contact (e.g., transient, short-term, or long-term), and (3) the device materials. The ISO standard contains a table of suggested tests related to the nature and duration of contact for the safety evaluation of medical devices made of polymers, metals, alloys, ceramics, or other nonviable materials. Until such time that the guidance incorporates additional suggested tests for other materials, such as biologicals, the applicant should use judgment in adapting the table to other materials.

2. A number of safety issues have been raised regarding exposure to electromagnetic energy, some or all of which may be relevant to a particular device. These areas of concern include, but are not necessarily limited to, teratogenesis, reproduction, genotoxic effects, cellular proliferation, and possible carcinogenic initiation/promotion effects. The sponsor should be cognizant of several epidemiological studies which have suggested some degree of association between electromagnetic field exposure and cancer incidence. It is incumbent upon the applicant to provide the data or other relevant material, such as a risk analysis, that will enable the agency to make a decision regarding the safety of the device. At a minimum, the applicant should provide the results of the following types of studies to document safety:

    a. Chronic Exposure Study Chronic toxicity tests are designed to both produce a toxic effect and define a safety factor. The chronic exposure study defines the etiology of an adverse response and determines the safety margin between the proposed exposure level and toxicity. The animal exposure time selected should be based on the typical duration of the BGS device usage for the clinical indication being studied, and associated safety factors. Specific endpoints to be examined should include, but not necessarily be limited to, complete blood chemistries, measures of behavioral function and complete necropsy results at the termination of exposure.

    *b. Reproductive Function Study The effects of exposure on reproduction should be investigated in at least two generations.

    *c. Teratology Study The gestational effects of exposure should be investigated using standard teratological measures.

    * These safety studies may not be necessary if the device is contraindicated for use among pregnant women and women who are planning to become pregnant.

    d. Genetic Toxicology Study The effects of exposure should be investigated using standard genetic toxicology procedures that, due to lack of available *in vitro* dosimetric procedures, all *in vitro* results should be correlated to at least one quantifiable biological endpoint (e.g., increases in RNA or DNA synthesis, cell proliferation, etc.). These effects should not be attributable to thermal perturbation of the experimental system.

3. Unless patients with metallic implants and cardiac pacemakers are specifically excluded from the clinical study patient population, the sponsor should provide preclinical data which establishes the safety of the use of the device with these implants.

B. Effectiveness

1. The device conformation and the animal model used for the *in vivo* preclinical efficacy assessment should approximate the intended device conformation and the clinical indication in the study. For example, a rabbit fibula defect without fixation model may not be appropriate if the device will be used to treat spinal fusions where instrumentation is indicated. If the device is intended to treat a condition for which an animal model exists, such a model system should be used to demonstrate the potential effectiveness of the device. Alternative animal models may be explored, when adequately supported by the literature. In the absence of an animal model system to demonstrate potential effectiveness, the sponsor should provide a clear scientific rationale to support the basis for initiating a clinical trial.

2. Biomechanical testing of the healed fracture should be performed and comparisons made to the biomechanical properties of the native bone.

CLINICAL DATA

The purpose of this section is to assist sponsors in developing an adequate protocol for use during the clinical trial. In order to obtain an approved IDE for a significant risk device, the clinical protocol, which is part of the investigational plan, should be presented to an IRB and to CDRH. The data obtained under the IDE should establish reasonable assurance of device safety and effectiveness in order to subsequently obtain PMA approval. 21 CFR 812.25 and the "Premarket Approval (PMA) Manual" include the required elements of an investigational plan and the required clinical data to be included in an IDE and PMA, respectively.

The clinical protocol should begin with an objective which clearly states the purpose of the study. Next, the protocol should clearly list the major characteristics of the study (number of patients, number of investigators, number of investigational sites, study duration, patient inclusion criteria, patient exclusion criteria, success/failure criteria, etc.) and include the data collection and reporting procedures which will be used to determine whether the device is safe and effective for its intended use. The clinical study should be designed and conducted in a manner such that it provides data which will constitute valid scientific evidence within the meaning of 21 CFR 860.7.

It is important to note that this is a clinical trial to provide data to support a finding of reasonable safety and effectiveness of a device and not merely a compilation of available patient records. Proper monitoring of the study, collection of data, accountability for all patients, and documentation and evaluation of reasons for discontinuation are essential. In developing a clinical protocol, the sponsor should carefully consider the "Statistical Guidelines for a Premarket Approval Application (PMA)" (see Bibliography). This document, although of a general nature, identifies many extremely important considerations and concepts relevant to study design, selection of appropriate control groups, data analysis, etc.

In a clinical trial to evaluate the efficacy of a BGS device for treating established non-union fractures, the patient can serve as his/her own control. The assumptions underlying this approach are that: 1) at nine months or more post injury, other conventional therapies already would have been attempted and proven unsuccessful for this patient, 2) there has been no evidence of progression in healing; that is, no radiographic signs of callus formation, and 3) there have been no intervening surgical procedures within the

three-month period immediately preceding device use. For conditions other than non-union, the sponsor should utilize concurrent controls and, where scientifically and ethically feasible, a randomized double-masked clinical design should be performed. In all cases, success should be demonstrated in terms of both radiographic and clinical healing.

Several IDE options are available to sponsors of clinical studies of BGS devices. These alternatives represent varying degrees of complexity in the types of questions being asked. When new modalities and/or new uses are being investigated, where enough safety information is available so that a safety profile can be defined for the device, a sponsor can submit an IDE for a small feasibility or pilot study. The scope and objective of this type of study are limited. For example, this type of study may be performed to optimize the device design, validate new measuring tools, identify clinically meaningful endpoints, or to obtain information on which to base the design of a larger, pivotal study. However, even though it is not possible to obtain statistical significance from such small studies, a limited evaluation of the data should be made to determine the relative clinical effectiveness in the index population studied. Sponsors should refer to th*e Guidance on the Review of Investigational Device Exemptions (IDE) Applications for Feasibility Studies*, IDE Guidance Memorandum No. 89-1.

Many factors exist that should be taken into consideration when designing the clinical protocol. Decisions such as when to include a concurrent control group, the appropriate length of follow-up, the type of data to be collected, i.e., continuous or discontinuous, etc., may be affected. The following list provides some examples of such factors:

Fracture age:	fresh, delayed union, non-union
Fracture type:	simple, comminuted, complex
Fracture location:	long bone (tibia, femur, etc.) flat bone (pelvis, cranium, etc.) spine: (lumbar, cervical, etc.)
Study objective:	demonstration of success rate (i.e., percentage healed) demonstration of a reduction in time to heal
Fracture management:	internal fixation, external fixation, casting

At a minimum, a typical clinical protocol should address the following in a detailed manner:

1. As stated previously, the clinical protocol should begin with a clearly defined objective. This should include a precise, medically accepted definition of the condition to be treated and a scientifically sound rationale for the proposed clinical study. Preferably, the objective should be stated in terms of the specific study endpoint(s) and outcome(s), and the parameters used to measure the success/failure of the device. The study should then be designed to fulfill this objective.

2. A complete definition of the study population should include the following:

    a. The patient inclusion criteria should be chosen to reflect the objective of the study. For example, a non-union study would include patients whose fractures have not healed for a minimum of nine months and who have not undergone surgical intervention during the previous three months. Documentation of previous fracture management, such as immobilization (type and duration) and surgery (type(s) and date(s)) help to establish the eligibility of a patient. In general, the inclusion criteria should incorporate objective measures, specific for the clinical indication being studied, for establishing patient eligibility.

b. The patient exclusion criteria should be chosen to eliminate all patients for whom bone growth stimulation is contraindicated and, to facilitate statistical analysis of the data by focusing the study population to a group with limited variability in baseline characteristics (see item 2e. below). Some contraindications to consider would be pathological fractures due to malignant tumors, synovial pseudoarthrosis, congenital pseudoarthrosis, active osteomyelitis, pregnancy, skeletal immaturity, and the presence of a cardiac pacemaker. Patients with the following conditions should also be excluded from the study unless adequate justification for their inclusion is provided: moderate to severe osteoporosis, diabetes, and renal dysfunction. The exclusion criteria should also incorporate objective measures, specific for the clinical indication being studied, for establishing patient eligibility. It is recognized that the contraindications may vary depending on the device and the treated indication.

c. The type of control and the ratio of control to treated patients to be used in the study should be identified and clearly defined. A randomized, concurrently controlled study design should be used. However, as stated previously, a concurrent control group may not be necessary for non-union studies. Justification for comparability of the control group to the experimental patient population should be given. Also, the method used to assign patients to the treatment or control group should be specified.

d. The proposed number of investigators, number of investigational sites and total number of patients should be specified. Patient numbers should be distributed evenly among investigators. Each investigator should treat an adequate number of patients to allow for the detection of low incidence complications. Also, inadequate and/or unequal patient numbers per investigator may decrease the probability that the patients for a given investigator will be representative of the study population. This may preclude the pooling of data between investigators and/or sites.

e. A statistical justification should be provided for the proposed number of patients to be enrolled in the study, including control patients. This number should be based on the ability to detect clinically and statistically significant differences between the treated patients and the control group with a given power, taking into consideration the expected withdrawal/lost to follow-up rate. Consideration should also be given to the number of strata in the study, particularly in designing feasibility studies. To assure that the data can be pooled, it is recommended that, initially, few strata be incorporated in the design. For example, allograft versus autograft use, one versus two or multi-level spinal fusions, etc. Factors that could increase the potential for variability include, but are not limited to, differences in dose, fracture type, fixation method, weight-bearing schedule, physical therapy and rehabilitation protocol, concomitant medications, and baseline status. If pooling of the data cannot be justified at the PMA stage, a subgroup analysis may be beneficial, using subgroups which are pre-defined in the IDE protocol.

3. The specific parameters to be assessed in the study should be completely described, including the measuring tool to be used and how the scores will be assigned and interpreted. For example, among the parameters to be assessed in a non-union fracture protocol would be pain and motion at the fracture site, presence or absence of the fracture line, number of cortices bridged by the callus, and presence or absence of trabeculae crossing the fracture. It is recognized that these parameters may vary depending on the indication and the treatment modality.

4. All aspects of the treatment protocol should be clearly defined including the following:

    a. Complete specifications for the treatment signal to be used in the study should be provided, as described above. If the device output is individualized for each patient, the applicant should describe how the delivered stimulation will be maintained within the target values of the protocol. A description of the applicator placement and the geometry of each treatment site should also be provided.

    b. The schedule, frequency, and duration of individual treatments, and the total treatment duration should be specified. Adequate justification, based on preclinical studies performed with the device, should be provided.

    c. Any additional patient care procedures to be employed during the treatment period (e.g., surgery, rehabilitation, immobilization, weight bearing, etc.) should be detailed. In addition, any permissible exception to the treatment protocol to accommodate individual patient conditions should be justified within the context of the study objective. It is extremely important that the influence of any concurrent and/or prior procedures on the treatment outcome be discussed, and provisions made in the study design to account for this influence when evaluating the effectiveness of the BGS device. In the case of a non-union fracture, the device should not be used within a three-month period following the last surgical intervention.

    d. Any salvage procedures to be employed in the event of treatment failure should be specified.

5. All aspects of the treatment evaluation should be clearly defined including the following:

    a. Fracture healing should be evaluated at regular intervals during the treatment and follow-up periods. The schedule of these evaluations as well as the duration of the follow-up period should be specified and adequately justified. For studies of non-union, CDRH recommends that all patients be followed for at least 1 year beyond the end of stimulus treatment to document any device-related complications prior to marketing approval. However, different long-term follow up periods may be necessary depending on the clinical indication being studied. For example, a study involving fresh fractures may require a shorter long-term follow-up period, whereas a period longer than 1 year may be required for a spinal fusion study.

    b. The method(s) used to evaluate the stimulation treatment should be detailed. The evaluation of pain and motion at the fracture site, generally assessed clinically by stressing the bone, should be standardized among clinical investigators. Objective scores for assessing these clinical parameters should be used. whenever possible. For parameters which are assessed radiographically, four radiographic views, e.g., AP, lateral, and two oblique, are suggested. In order to minimize investigator bias, all x-rays should be independently reviewed by a masked, board-certified radiologist or orthopedist with experience in evaluating fracture radiographs.

    c. The final criteria for success and failure both for the patient and for the study should be precisely predefined and clinically acceptable. Success should be demonstrated in terms of both radiographic (e.g., absence of fracture line, bridged cortices, etc.) and clinical healing (e.g., reduction of pain, improvement in function, etc.). Both the objective and subjective bases for the determination of success should be clear and consistent among all investigators and patients. The criteria should be defined in terms of the endpoints and the parameters used to measure them. Quantitative definitions of success, i.e., specific success/failure criteria, should be established for all outcome measures. For example, the specific postoperative pain improvement required for a patient to be a success, should be defined and adequately justified.

d. A rationale and description of the statistical analyses to be employed in assessing the effectiveness of the treatment should be provided. This should include an appropriate statistical comparison of the treated patients to the control patients for all evaluation parameters. Statistical evidence of device effectiveness is essential. However, this alone is not sufficient for PMA approval. Sponsors should demonstrate both statistical and clinical significance.

   If any interim analyses are to be performed, this must be taken into account in designing the study. The level of statistical significance (p) chosen for the analysis(es) should be specified. The sponsor should define and adequately justify the stopping rule(s) to be applied in terms of overall patient success.

6. Sample patient case report forms should be submitted in the IDE application. These should include the following:

   a. a pre-treatment evaluation form detailing the patient eligibility and previous fracture management information;

   b. treatment evaluation forms, to be used at each scheduled time point to allow for a record of patient compliance, detailing the patient baseline characteristics, date of treatment onset, treatment schedule, any additional patient care procedures, including pain medications and other medications taken, and the recording of the treatment outcome measures at each visit;

   c. a form for reporting of all complications and adverse events; and

   d. forms to report withdrawals and patients lost to follow-up.

7. Additional information required in the investigational plan of an IDE, as outlined in 21 CFR 812.25, includes:

   a. a risk analysis;

   b. a description of the monitoring procedures;

   c. copies of all consent materials;

   d. IRB information; and

   e. all records and reports maintained by the investigator(s) and the sponsor.

8. All investigational (draft) labeling for the device including, but not limited to, the following:

   a. an indication statement reflecting the intended use of the device;

   b. a list of warnings, precautions, and contraindications for the device which reflects the study's inclusion/exclusion criteria, and the potential risks discussed in the Risk Analysis section;

   c. a statement that the use of the device is investigational for the proposed indication as follows: "CAUTION -Investigational Device. Limited by Federal (or United States) law to investigational use";

   d. samples of all labels to be used with the device; and

e. detailed instructions and illustrations which are adequate to direct the patient and physician in the proper use of the device. These instructions should include: application of the device, any alterations needed to personalize the device for particular individuals, an explanation of each console control and indicator, and operating instructions for the specific indication. Depending on the nature of the device, it may be necessary to include separate instructions for the physician and the patient.

CONSIDERATIONS FOR THE PMA APPLICATION

At the time of the PMA submission, the sponsor should submit all information generated in the IDE study. The sponsor should consider the following when preparing the PMA submission:

1. Pooling data from different investigators and investigational sites should be adequately justified. This justification should show that the patients have sufficiently similar baseline characteristics, that the patients for each investigator were not significantly different with respect to the population description, fracture management, incidence of complications, and number of patients withdrawn or lost to follow-up.

2. The evaluation of protocol violations, patient compliance, patient withdrawals and patients lost to follow-up should be documented. Rationale should be given for categorizing these patients as other than treatment failures. The sponsor should also document all efforts made to relocate patients who are lost to follow-up.

3. In addition to submitting summaries of the patient descriptive data and the results of all statistical analyses, the PMA application should report adverse reactions and complications, patient discontinuations, patient complaints, device failures and replacements, and organized tabulations of data from all individual subject report forms. Additionally, copies of such forms should be provided for each subject who died during the clinical investigation or who did not complete the investigation.

4. It is strongly recommended that an intent-to-treat analysis, i.e., one which accounts for all patients enrolled in the study, be included as part of the statistical evaluation. Depending on the duration of the treatment before each patient withdrawal, patient loss to follow-up, or patient non-compliance, these patients may or may not be included in all final primary analyses of treatment success. Regardless of the length of time the patients, i.e., withdrawn or noncompliant, were enrolled, they should be followed for potential adverse events.

Specific questions and clarification regarding this guidance for BGS devices can be addressed by contacting DGRD at 301-594-2036.

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