Guidance Document for Testing Biodegradable Polymer Implant Devices (Text Only)

This guidance was written prior to the February 27, 1997 implementation of FDA's Good Guidance Practices, GGP's. It does not create or confer 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. This guidance will be updated in the next revision to include the standard elements of GGP's.

DRAFT

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PLEASE FORWARD YOUR COMMENTS TO:
Orthopedic Devices Branch
Division of General and Restorative Devices
Center for Devices and Radiological Health
U.S. Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993

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II. PREFACE

The purpose of this document is to recommend to the device manufacturer or sponsor of a future premarket notification (510k), Investigational Device Exemption (IDE), Premarket Approval (PMA) application, reclassification petition, or master file important information that should be provided to the FDA so that the FDA will be able to determine the substantial equivalence and/or safety and effectiveness of biodegradable orthopedic fracture fixation implant devices (e.g., plate, pin, screw).

Suggestions and recommendations presented in this document are not mandatory requirements, but reflect data and methodologies which the Office of Device Evaluation (ODE), Division of General and Restorative Devices (DGRD) has determined to be acceptable. In this context, several points should be remembered:

1. The guidance document is primarily intended to include scientific recommendations. Therefore, it suggests some important evaluation criteria, test procedures and end points. There may be circumstances where an alternative method or additional information may be useful and this document has included some examples. If the manufacturer or sponsor can answer the same scientific issues by means other than those included in this guidance document, they should feel free to do so. Because the scope of this document does not specify any particular type of bone/suture anchor device, some of the recommended test methods may need modification to address the properties of a particular product.
2. The guidance document should be viewed as a living document. As scientific knowledge changes and scientific techniques are improved, FDA will periodically revise the document.

III. LABORATORY TEST METHODS

All evaluations should be performed on sterilized materials. The storage time and environment of each sample since manufacture should be reported.

ANALYSIS OF THE MATERIALS

The composition and material structure (e.g., phases, reinforcement, matrix, coating) of the product to be implanted should be characterized quantitatively. These analyses may include the following:

- COMPOSITION AND MOLECULAR STRUCTURE
- main ingredients
- trace elements (e.g., heavy metals
- catalysts
- low molecular weight (MW) components (separate components which have and have not

chemically reacted with the polymer, e.g., contaminants, curing agents, crosslinking agents, dyes, monomer/dimer content, plasticizers, residual solvents)

- polymer stereoregularity and monomer optical purity (if the monomer is optically active)
- polydispersity, number average molecular weight (M_n), weight average molecular weight (M_w) (2 out of 3)
- molecular weight distribution (MWD)
- intrinsic (or inherent) viscosity (specify solvent, concentrations and temperature)
- whether the polymer is linear, crosslinked or branched
- copolymer conversion (e.g., block, random, graft)
- polymer blending
- MORPHOLOGY (SUPERMOLECULAR STRUCTURE)
- % crystallinity
- orientation of phases/macromolecules
- types and amounts of phases
- COMPOSITE STRUCTURE
- laminate structure
  - thickness of each ply
  - number of plies
  - orientation and stacking sequence of plies
  - symmetry of the layup
- position of reinforcement within the matrix
  - location within the part
  - 3 dimensional orientation
  - fiber density (e.g., distance between reinforcement components or reinforcement:matrix volume and weight ratios)
  - fiber contacts and cross-overs per mm
- reinforcement structure
  - cross-sectional shape
  - surface texture and treatment
  - dimensions

  - fiber twist
  - denier
  - weave
- coating
  - total number of coating layers
  - thickness of each layer
  - voids
    - mean volume percent
    - interconnections
    - penetration depth and profile
  - drawing or photographs of the product illustrating the position of the coating and any variation in coating thickness
- **PHYSICAL PROPERTIES**
- dimensional changes of the material as a function of time
- densities of reinforcement, matrix and composite
- mass of the smallest and largest sizes
- roughness of all surfaces
- surface area of the smallest and largest sizes
- dimensioned engineering drawings of any nonrandom surface structure patterns (e.g., machined structures)
- **THERMAL PROPERTIES**
- crystallization temperature
- glass transition temperature
- melting temperature

STRENGTH RETENTION TESTING

GENERAL COMMENTS

Mechanical properties are most important because they determine whether the fracture site is adequately fixed to avoid loosening, motion and nonunion. Weight loss and inherent viscosity measurements are optional and may be helpful in screening different materials and in

understanding degradation mechanisms, though they may not directly address the mechanical properties of the device.

In the in vitro degradation (or strength retention) test, samples are placed under a load in a physiologic solution at 37 degree C. Samples are periodically removed and tested for various material and mechanical properties at specified intervals (typically 1, 3, 6, 12, 26, 52 and 104 weeks) until strength has dropped below 20% of the initial strength.

In vitro aging might be easier to perform and control than in vivo aging, but in vitro conditions do not include the effects of cells, enzymes and other variables. The in vitro degradation rates should be validated by comparing to the in vivo degradation rates so the in vitro test results can be extrapolated to clinical conditions. Samples should be implanted in an animal model and mechanically tested (as outlined in this section) to determine if there are any significant difference in the outcome of test samples degraded in vitro and in vivo.

Test specimens may be either the product to be implanted or test coupons. The former is preferred unless there is quantitative data which adequately addresses size and surface area considerations in relating in vitro degradation of test coupons to in vivo behavior of the clinical implant. The test specimen model or size which degrades the fastest (e.g., due to a higher surface area or higher stresses) should be evaluated as a worst case. Testing is not required for a device which differs in geometry or dimensions compared to tested samples if it is demonstrated that there is no significant difference in the strength retention test results.

The degradation of the mechanical properties of the test device is compared to a predicate device. The devices are implanted either at the site of actual loaded use or at a nearby site. A range of healing time for the indicated repair should be provided from the literature. The implantation time should be at least twice as long the longest time over which healing of the repair is expected to occur. Data for this set of tests may be from the same animals used in other tests.

DESCRIPTION OF THE TEST SETUP (ENVIRONMENT)

The test solution composition should be justified. For example, bovine serum or phosphate buffered saline solution in a volume at least 20 times the volume of the test sample may be used. Unless a special effect is to be simulated (e.g., infection), the pH of the solution should approximate the pH of a physiologic environment (about 7.4) kept sterile and properly buffered or changed periodically. Additives may be required to inhibit the growth of bacteria and other microbes during the test period. The pH of the soaking solutions should be measured at each specified test interval, or once per month, whichever is shorter. Samples should be discarded if the measured pH is outside the specified value of more than ± 0.2. Each sampling container should be sealable against solution loss by evaporation. Each test specimen should be kept in separate containers and isolated from other specimens to avoid cross contamination of degradation byproducts.

Samples are fully immersed in the physiological solution at 37 degree C (or above for the purpose of accelerated testing) for the specified period of time. One group of samples are stressed during the entire time in solution to simulate clinical worst case conditions while another group of samples are set-up in the same environment (including fixtures) as the first group, without stressing. Cyclic loading of the stressed group is preferable, though not required. The amount of sample agitation, solution flow past test specimens, frequency that the solution is replaced and the clinical significance of these factors should be reported.

DESCRIPTION OF SPECIMEN ANALYSIS

Mechanical Testing

The degradation of the mechanical properties of the submitted device over time is compared to the same changes for a predicate device. For example, pull-out tests may be used to test a bone anchor implanted into cadaveric bone or foam bone analogs. If cadaveric bone is used, the implantation sites should correspond to those intended for the submitted device. If foam bone analogs are used, the density of the foam should be compared to the density of the bone it is intended to model. The degradation values should be validated to in vivo results.

At each specified time period throughout the duration of the immersion/loading time, samples are removed and tested. Unless otherwise deemed relevant, samples should be tested in a non-dried or 'wet' condition. Unless specifically germane to the testing scheme, samples should be retired after the completion of each test.

Weight Loss

Test samples should be weighed to an accuracy of 0.1 % of the total sample weight prior to placement in the physiological solution. Upon completion of the specified immersion/loading time, each sample should be removed and dried to a constant weight. Drying conditions may include enclosure in a desiccator at STP, use of a partial vacuum or the use of elevated temperatures. The weight should be recorded to an accuracy of 0.1 % of the original total sample weight. Elevated temperatures may be used to assist drying of the sample provided that the temperature used does not change the sample. The drying conditions used to achieve a constant weight should be stated.

Molecular Weight

The inherent viscosity (logarithmic viscosity number) or some other justifiable method (e.g., GPC) is measured prior to placement of samples in the physiological solution. Samples should be removed from immersion and loading at each specified time period throughout the duration of the test and tested for inherent viscosity as above. Dilution ratio in g/ml should be reported.

SHELF LIFE

The shelf-life of the final product should be determined.

BIOCOMPATIBILITY

Material formulations or combinations with limited or no history of safe use as orthopedic implants should demonstrate a biological response at least as good as a predicate or substantially equivalent device when tested according to the ISO TC150 for Medical Devices and in an appropriate animal study. As part of the analysis, the degradation by-products and their metabolic pathways should be identified.

In vivo strength of repair studies are intended to compare the mechanical strength of intact tissue to that of a tissue repaired using the device under review or a predicate device. A range of healing times for the indicated repair should be provided from the literature. The implantation time should be at least twice as long the longest time over which healing of the repair is expected to occur. These studies should determine the degree to which the implant results in inhibition of osteogenesis, resulting in weaker bone, lack of tissue apposition, pseudoarthrosis, etc. The animal implant site should simulate the tissue site for which the device is intended for clinical use. A histological analysis should assess bone remodeling/strss shielding, profgressive degradation/absorption of the material, focal proliferation and subsequent disappearance of cellular elements responsible for degradation/absorption and the replacement of the device by new bone growth at the implant site with time. The time till most of the device (at least 90%) is absorbed and replaced by bone should be determined and the time till 100% absorption estimated by extrapolation.

Histology of the implant site is important to determine the tissue response, normal and abnormal, to the presence of the device and its breakdown products. The submitted device should be implanted into an animal model such that it experiences loading. For example, if the device is a bone anchor, the suture should pull on the device. The study should extend out to one year with comparative analyses made at appropriate intermediate time points.

IV. CLINICAL DATA AND LABELING

Clinical data may be required if the intended use, materials, design or some combination of these differ significantly from a legally marketed predicate device.

Labelling may require a warning concerning site to site variation in blood flow and hence, degradation rate. Users should also be warned of possible adverse reactions (e.g., compliment activation as reported in Tegnander, A.; et al.: 'Activation of the Complement System and Adverse Effects of Biodegradable Pins of Polylactic Acid (Biofix) in Osteochondritis Dissecans'. Acta Orthop. Scand., 65, pp. 472-475, Aug., 1994).

V. MANUFACTURING

The manufacturing process of the final product and test samples should be described in enough detail to give a general understanding of the origin of the structure as characterized above.

VI. REPORTING

To help FDA in its review and facilitate a determination of substantial equivalence and/or safety and effectiveness, a very brief summary of all information should be organized in the order shown in part VII. ORGANIZATION OF REPORTED INFORMATION. Any additional and important information not specifically mentioned in the above guidance document should be inserted into this organization where appropriate. Detailed test reports from which the summarized data originated should be organized in a similar manner (as much as possible) and included in the submission to FDA. The detailed reports should include, but are not limited to the following:

1. Report title
2. Investigators' names
3. Facility Performing the test
    - Name
    - Address
    - Phone Number
4. Dates
    - Test initiation
    - Test completion
    - Final report completion
5. Objectives/Hypothesis
6. Test and control samples
    - Sample selection criterion
    - Design
    - Materials
    - Processing methods
    - Differences between test samples, control samples and marketed device
7. Methods and Materials
    - Test setup schematic or photograph
    - Description of grips or potting medium interfacing with samples

- List of dependent, independent and uncontrolled variables, e.g.:
  - Test and control sample parameters
  - Environment composition, pH, volume, flow, temperature, replacement
  - Electromagnetic fields, applied charges, irradiation
  - Load directions, points of application and magnitudes
  - Times (e.g. rates, frequencies, number of cycles)
  - Other
- Rationale for choices of parameters, values, etc.
- Methods of specimen examination (e.g., failure analysis)
- Statistical justification for the number of samples
- Chronological description of the test procedures
- Deviations from referenced protocols and standards

8. Results
   - Time from manufacturing till testing commences
   - Discussion of the data and possible mechanisms
   - List of conclusions
   - Discussion of the objective/hypothesis
   - Simplifications and assumptions made and clinical implications of results
9. Appendices
   - Experimental data
   - Calculations
   - Bibliography of all references pertinent to the report.

Name: ABS Date: Ap. 20, 1996

VII. ORGANIZATION OF REPORTED INFORMATION

PROPERTY/COMPONENT	POSSIBLE PARAMETERS	EXAMPLES OF TEST METHODS
CHEMICAL COMPOSITION	MAIN INGREDIENTS	NMR, GC, HPLC
	PURITY OR TRACE ELEMENTS	RESIDUAL IGNITION, AA, ICP
	CATALYSTS	AA
	LOW MW COMPONENTS WATER SOLVENT	GC, HPLC, IR, GPC, NMR KARL-FISCHER TITRATION GC HEADSPACE
	STEREOREGULARITY & MONOMER OPTICAL PURITY	POLIMETER (OPTICAL ROTATION)
MOLECULAR STRUCTURE	POLYMER BLENDING BRANCHED, LINEAR, CROSSLINKED COPOLYMER BRANCH LENGTH COPOLYMER CONVERSION Mn, Mw, POLYDISPERSITY MWD	NMR, GPC SOLUBILITY, SWELLING, VISCOSITY HIGH RESOLUTION NMR NMR GPC, ASTM D3593 GPC, ASTM D3593
MORPHOLOGY (SUPERMOLECULAR STRUCTURE)	% CRYSTALLINITY	X-RAY DIFFRACTION, DSC, DTA
	TYPES AND AMOUNTS OF PHASES	OPTICAL MICROSCOPY, BIREFRINGENCE
	ORIENTATION OF PHASES	X-RAY DIFFRACTION, DRAW RATIO
COMPOSITE STRUCTURE	LAMINATE STRUCTURE	THICKNESS OF EACH PLY NUMBER OF PLIES ORIENTATION AND STACKING SEQUENCE SYMMETRY OF THE LAYUP
	REINFORCEMENT POSITION	LOCATION WITHIN THE PART 3 DIMENSIONAL ORIENTATION VOLUME OR WEIGHT FRACTION CONTACTS, CROSS-OVERS, HOMOGENEITY
	REINFORCEMENT STRUCTURE	CROSS-SECTIONAL SHAPE SURFACE TEXTURE AND TREATMENT DIMENSIONS FIBER TWIST DENIER WEAVE (TYPES, ENDS/MM)
	COATINGS	TOTAL NUMBER OF COATING LAYERS THICKNESS OF EACH LAYER VOIDS MEAN VOLUME PERCENT INTERCONNECTIONS DEPTH & PROFILE POSITION OF THE COATING VARIATION IN THICKNESS
PHYSICAL PROPERTIES	WATER ABSORPTION	ASTM D570
	DIMENSIONAL CHANGES	ASTM D1042
	DENSITY	ASTM D792
	POROSITY DISTRIBUTION: SIZE LOCATION	POROSIMETRY, MICROSCOPY
	LEACHING OF LOW MW MOLECULES	
	MASS OF THE SMALLEST & LARGEST SIZES	
	ROUGHNESS	
	SURFACE AREA OF THE SMALLEST & LARGEST SIZES	

	SURFACE STRUCTURE PATTERNS	
THERMAL PROPERTIES	CRYSTALLIZATION TEMPERATURE GLASS TRANSITION TEMPERATURE MELTING TEMPERATURE	ASTM D3418 ASTM D2117

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PROPERTY/COMPONENT	POSSIBLE PARAMETERS	EXAMPLES OF TEST METHODS
ELASTIC MODULUS OR RIGIDITY	HEALING RATE AND OSTEOPOROSIS	ASTM D671
CYCLIC FATIGUE	FRACTURE, DEFORMATION, WEAR & LOOSENING	SEE APPROPRIATE STANDARDS
FRACTURE MECHANICS	CRACK PROPAGATION	
STATIC STRENGTH	FRACTURE/LOOSENING	ASTM D638, D695
LOCAL STRESS RISERS, RESIDUAL STRESS	EFFECT OF HIGH STRESS ON THE ENDURANCE OF THE DEVICE	STRESS ANALYSIS &/OR MECHANICAL TESTING
VISCOELASTICITY	LOOSENING	CREEP, ASTM D2990 STRESS RELAXATION, ASTM D2991
WEAR & DEGRADATION	EFFECT OF STERILIZATION	USE STERILIZED SAMPLES FOR ALL EVALUATIONS OR DEMONSTRATE NO SIGNIFICANT EFFECT ON ALL PROPERTIES
	EFFECT OF CONTACT WITH OTHER IMPLANTS (E.G., BONE CEMENT)	
	SHELF LIFE	
	STRENGTH RETENTION AFTER CYCLIC LOADING IN 37°C SALINE	AGE SAMPLES & MEASURE: MECHANICAL PROPERTIES DEFECTS, WEIGHT LOSS MW, DIMENSIONAL STABILITY
	FRACTURE/LOOSENING	FRETTING & DEGRADATION
BIOCOMPATIBILITY	BULK MATERIAL, PARTICLES, BREAKDOWN BY-PRODUCTS, METABOLIC PATHWAYS	
CLINICAL DATA	UNFORESEEN PROBLEMS	
OTHER	NEW FAILURE MECHANISMS	LOOK FOR & EVALUATE NEW FAILURE MECHANISMS CLINICAL STUDY

More in Guidance Documents (Medical Devices and Radiation-Emitting Products) (/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm)

Cross-Center Final Guidance
(/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm081752.htm)

Office of Compliance Final Guidance
(/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070269.htm)

Office of the Center Director Final Guidance
(/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm110228.htm)

Office of Communication and Education Final Guidance
(/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070271.htm)

Office of Device Evaluation Final Guidance 2010 - 2016
(/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm198577.htm)

Office of Device Evaluation Final Guidance 1998 - 2009
(/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070272.htm)

Office of Device Evaluation Final Guidance 1976 - 1997
(/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080283.htm)

Office of In Vitro Diagnostics and Radiological Health Final Guidance
(/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070274.htm)

Office of Surveillance and Biometrics Final Guidance
(/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070275.htm)

Office of Science and Engineering Laboratories Final Guidance
(/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070277.htm)

Draft Guidance
(/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm407274.htm)

Radiation-Emitting Products Guidance
(/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm283507.htm)

Withdrawn Guidance
(/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm425025.htm)