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DRAFT GUIDANCE FOR THE CLINICAL INVESTIGATION OF URETHRAL STENTS

Urology and Lithotripsy Devices Branch
Division of Reproductive, Abdominal, Ear, Nose and Throat
and Radiological Devices
Office of Device Evaluation
Center for Devices and Radiological Health

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I. PREFACE

This guidance document identifies the features of a clinical investigation that the Food and Drug Administration (FDA) would find acceptable in support of investigational device exemptions (IDE) applications for clinical studies of urethral stents. It is intended to be generic and broadly applicable to various intended uses and urethral stent designs. It is important to understand that certain intended uses may not require all of the information contained herein, whereas other intended uses may require additional information beyond the scope of this guidance document. It is also important to understand that this draft guidance is intended to identify the basic questions raised by sponsors developing urethral stents. It is not intended to replace interactions with FDA to address questions about a specific product; it does however, provide a framework for sponsors of devices being developed in this area. This guidance was developed based on information contained in previous IDE and PMA applications for similar products as well as a review of the published literature.

The November 11, 1994, "Draft Guidance for the Clinical Investigation of Devices Used for the Treatment of Benign Prostatic Hyperplasia (BPH)" may be useful for BPH indications of urethral stents. A copy of that guidance document may be obtained from the Division of Small Manufacturers Assistance (DSMA) by telephone at (800) 638-2041 or (301) 443-6597, or by letter at the following address: Division of Small Manufacturers Assistance (HFZ-220), Center for Devices and Radiological Health, Food and Drug Administration, 1350 Piccard Drive, Rockville, MD 20850.

Applicants should submit any IDE in accordance with FDA's "Investigational Device Exemption (IDE) Manual." This manual is also available upon request from DSMA.

II. DEVICE DESCRIPTION

The material composition of the urethral stent should be fully characterized. This characterization should include an identification of any impurities present in or on the finished samples. Diagrams of the stent with all dimensions and its component materials distinguished should also be provided. Multiple diagrams

may be necessary to show adequate detail. A written description of the device design should accompany these figures. A description of all urethral stent accessories and their function(s) should also be provided.

III. PRECLINICAL TESTING

This section discusses testing necessary to support approval of an IDE application for a urethral stent; however, additional testing may be necessary depending on device design. All preclinical tests should be conducted in accordance with the Good Laboratory Practice (GLP) for Nonclinical Laboratory Studies regulation (21 CFR, Part 58). Any deviations from the GLP regulation should be fully described, and include a justification for accepting the results of these tests.

With the exception of the biocompatibility testing, the preclinical testing outlined below should be performed on device designs and size ranges representative of those proposed for use in the clinical study. For biocompatibility testing, the test protocols, all raw data sheets, and any other supporting data should be provided. All tests should be conducted on the final sterilized product.

A. Biocompatibility

Refer to the blue book memorandum #G95-1, "Use of International Standard ISO-10993, 'Biological Evaluation of Medical Devices Part-1: Evaluation and Testing'" (May 1, 1995) for information on biocompatibility testing. A copy of this memorandum may be obtained from DSMA.

Under this blue book memorandum, urethral stents implanted for long-term use are defined as permanent duration, implanted devices contacting tissue/bone. Urethral stent accessories, however, such as transurethral insertion instruments, are categorized as limited duration, surface (mucosal) contacting devices.

FDA believes the following biocompatibility tests should be considered and addressed for urethral stents: cytotoxicity, sensitization, mucosal irritation, systemic toxicity (acute), sub-chronic (sub-acute) toxicity, genotoxicity, implantation, chronic toxicity, and carcinogenicity. Deviations from these tests should be scientifically justified and based on available data concerning the specific materials proposed for use. It is not necessary that all of the long-term studies be completed prior to submission of the IDE.

(Note: the biocompatibility test categories may differ from those specified in this guidance, depending on the intended use and design of the device.)

B. Sterilization and Reuse of Accessories

The following information regarding the device's sterilization process should be provided: (i) the method of sterilization; (ii) the method/protocol used to validate the sterilization cycle; (iii) a description of the packaging materials; (iv) the residual levels of ethylene oxide, ethylene chlorohydrin, and ethylene glycol remaining on the device after the sterilization quarantine period (if applicable); and (v) the radiation dose (if applicable). Additionally, the method (e.g., LAL or rabbit test) used to routinely evaluate this device for pyrogenicity should be stated.

For urethral stent accessories that may be reprocessed and reused, please refer to the draft guidance "Labeling Reusable Medical Devices Reprocessing In Health Care Facilities: FDA Reviewer Guidance" (March 1995) for appropriate steps on labeling and validation of the recommended reprocessing instructions. A copy of this guidance may be obtained from DSMA.

C. Performance Testing

Data from testing which demonstrate that the device performs to specifications should be provided. The following information should be considered:

1. Manufacturing Specifications

   Components of the device should be independently tested to show that the manufacturing specifications have been met. For example, if the stent is composed of intertwined metal wires, the wires should be tested for tensile strength and elongation. Additional tests may be necessary depending on the device design. Any appropriate standards referring to the tested properties should also be discussed and satisfied.

2. Stent Uniformity

   The uniformity of the expanded stent should be determined by quantitative documentation after expansion in a tube and should be consistent with the labeled expanded diameter and length. Also, the change in stent diameter as a function of circumferential pressure should be determined.

3. Fatigue

   This set of tests should be designed to simulate the cyclic stresses, associated with body movement, that will be experienced by a urethral stent. The purpose of these tests is to show that the urethral stent can withstand the anticipated stresses over its expected operational lifetime. The appropriateness of the environment used (e.g., synthetic urine), the load applied, the rate of loading, direction and placement of the load, the predetermined performance criteria, and any other relevant parameters used in the tests should be provided.

4. Corrosion

   Corrosion testing is needed in order to assess the long-term effects of bodily fluids on the urethral stents. This testing should be performed in a natural or artificial medium (i.e., urine) that is chemically equivalent to the environment the urethral stent will face in vivo. The urethral stent should be examined for any visible corrosion product or encrustation and tested to determine changes in structural integrity. The device should also be measured for any weight change. The duration of the testing as well as any deviations from the above criteria should be justified.

5. Electrical Safety

   The safe interaction of the urethral stent with common electrosurgery devices should be demonstrated in appropriate pre-clinical tests (i.e., stent degradation, fracture, etc.).

6. Magnetic Resonance Imaging

   Any effect that the stent will have on MRI scans should be determined and discussed.

7. Other

   Other tests that measure properties such as deformability, tensile strength, thermal response of the material, etc., should be performed as the device function and design warrants. Any tests or quality control procedures performed to further characterize the mechanical function of the urethral stent should also be reported.

D. Animal Study

Testing on a minimum of six dogs should be provided for the device, with follow-up for 6 months on devices intended to be permanently implanted. Evaluation should include assessments of the following adverse events: stent migration, encrustation, erosion, pressure necrosis, urothelial hyperplasia, stone formation, urethral edema, cellular atypia, and device failure or breakage.

Fatigue testing similar to that discussed above in section III.C. should also be performed on the explanted stents in order to evaluate any changes to the structural integrity of the device that may have occurred due to stent implantation. Additionally, evaluations should be performed to support any assumptions made in the bench testing (e.g., Is the fluid medium used in the in vitro corrosion test an appropriate substitute for the actual test environment?).

The treatment parameters should closely approximate the intended use of the device in humans to: (i) demonstrate the safety of the procedure, (ii) evaluate the functional characteristics of the device design, and (iii) validate the performance of the device for its intended use. If appropriate, these tests should include: placement of a single urethral stent as well as the maximum number of urethral stents proposed for use in the clinical study; repositioning the device in vivo; and removal using the recommended techniques.

In order to independently evaluate the outcome, the following information should be provided:

1. the test protocol (including objectives and procedures);
2. the results (including the investigator's comments);
3. the conclusions;
4. a complete identification of each implantation site;
5. a report on all complications and device malfunctions; and
6. a discussion of the results as they relate to the human anatomy and the intended use of the urethral stent.

The results from serial sectioning and staining with Hematoxylin and Eosin stains (preferably evaluated by a independent pathologist to evaluate masked

histological samples) should be provided. The discussion of the histological examination of the treatment area should include micrographs and histological descriptions from a qualified practitioner. The histological examination should specifically include:

1. actual representative photographs of the microscopic histology whenever possible (due to the limited reproduction capabilities of photocopies); and

2. to demonstrate safety, microscopic review and histological descriptions of any changes in the rectal wall, bladder neck, external sphincter, and prostatic capsule.

Animal testing may not be necessary if appropriately justified. An appropriate justification should take into consideration device/material history of use and available data from prior animal studies, human clinical trials (foreign and domestic), or other appropriate studies performed under protocols that specifically address the issues outlined above.

IV. CLINICAL STUDY

While this document offers specific information regarding the design of a clinical trial for urethral stents, general guidance regarding clinical trials is available from DSMA in the guidance document entitled "Clinical Trial Guidance for Non-Diagnostic Medical Devices" (February, 1995).

A. Pilot Study

FDA may require a pilot study to ensure device functionality, monitor safety and basic effectiveness, and gain experience in using the device prior to commencing the larger clinical study.

A pilot study for urethral stents will generally be limited to 2 institutions and 20 patients. Data should be submitted on at least 10 patients followed for a minimum of 6 weeks before FDA will consider further expansion of the study. The schedule of follow-up examinations should be designed to ensure patient safety and to ensure that adequate safety and effectiveness data are collected (e.g., immediate post-treatment, 3 weeks, 6 weeks). The safety data should address all adverse events including: type, duration, severity, resolution, whether the event was related to the device, and uniform characterization of any tissue effects that may be caused by the urethral stent. Cystoscopic evaluation should address migration, epithelialization, irritation and all other effects to the implant site and surrounding tissue. Other methods such as radiologic studies may also be useful to determine

whether device migration occurred during follow-up. Where appropriate, effectiveness data should address symptoms, peak uroflow, voiding pressures, and residual urine.

The learning curve during the pilot study should be assessed by the investigators to help determine the number of procedures necessary for a physician to gain sufficient experience to properly implant the urethral stent, use its accessory devices, and manage insertion complications.

B. Clinical Study

To provide reasonable assurance of the safety and effectiveness of the urethral stent, a well-controlled, prospective, clinical study with a statistically justified sample size, clear investigational hypotheses, and detailed appropriate follow-up is essential.

Randomization of patients between the urethral stent and an appropriate control is recommended to help ensure that imbalances between study arms among known or suspected prognostic factors are minimized. Randomization also helps to protect the study from conscious or unconscious actions by the investigators that may lead to non-comparability (i.e., bias) and provides a probability basis for the statistical analysis.

1. Control Population, Study Design, and Sample Size

For the urethral stent, the use of a concurrent, masked control is recommended. Such an investigation should consist of an experimental treatment group (i.e., stent arm) and a control group which receives a standard, well characterized treatment. Each study group should be identically evaluated and followed. Although it is possible that patient blinding may not be possible, it is strongly recommended that follow-up investigators be masked as to the treatment received.

A study with an active, concurrent control is particularly useful when other surgical urological procedures, which in themselves are known to provide a therapeutic effect to the disease state under study, are performed during placement of the urethral stent. The control group outcome helps to assess whether the results are due to the urethral stent or such concomitant surgical urological procedures.

FDA will consider studies in which the patient serves as his own control, but this study must be designed to conclusively demonstrate that the treated disease is in a steady state before beginning the experimental

treatment. Data collection under this type of study design should continue for a sufficiently long duration prior to stent placement to demonstrate the stability of the disease. The study should minimize reliance on retrospective analyses and maximize prospective methods of demonstrating the steady state of the particular urological disease.

Other study designs include the use of historical data obtained from the literature. FDA is skeptical that available historical information is adequate due to likely variations in patient demographics, selection criteria, and evaluation methodologies.

The sizes of the treatment and control populations should be based on the expected probability of success for the two groups. The sponsor should determine the sample size needed to achieve a predetermined significance level with sufficient power to detect a predetermined minimal difference which is clinically meaningful for each of the hypotheses to be tested. The minimum sample size should be the largest obtained from the sample size calculations for testing each of the hypotheses in question so that a few patient losses will have less chance of invalidating the study.

2. Protocol

A detailed protocol for the clinical trial specifying explicit patient inclusion/exclusion criteria, clear study objectives, specific investigational procedures, and a well-defined follow-up schedule should be provided.

To minimize protocol deviations, the sponsor should closely monitor investigator conformance to the clinical protocol (e.g., patient selection, device insertion methods and intraoperative adjunctive procedures, completeness and timing of follow-up evaluations, etc.).

The protocol should be well designed to address all enrollment issues mentioned below since the patient may present with a condition at enrollment that could confound or adversely affect the study results. These patient conditions should be well documented at baseline and throughout the study.

3. Patient Inclusion/Exclusion Criteria

The study population should be defined prior to study initiation by development of rigorous and unambiguous inclusion/exclusion criteria. These criteria should uniquely characterize the study population for the

intended use of the device and define a homogeneous study population. The inclusion and exclusion criteria should also rule out those patients with concomitant conditions that may confound the results of the study and patients whose enrollment into the study would place them at an unreasonable risk.

Because this guidance is generic to all urethral stent applications, other appropriate specific inclusion and exclusion criteria relevant to the disease under study will likely also be necessary. Sponsors may modify the selection criteria listed below, if appropriate and acceptable justification is provided.

a. Patient Inclusion Criteria

1) within chosen age range(s) (e.g., ≥ 18 years);

2) within the targeted population, (e.g., failed prior treatments - unless the urethral stent is intended to be used and labeled as a first-line treatment);

b. Patient Exclusion Criteria

1) history of any illness or surgery that might confound the results of the study, which produces symptoms that might be confused with those of the disease process under consideration, or which poses additional risk to the patient (e.g., bleeding disorders);

2) confirmed or suspected malignant disease affecting the urinary tract;

3) previous pelvic irradiation or radical pelvic surgery if these make the probability of success unlikely;

4) active urinary tract infection (UTI);

5) medications that could affect the measurements under investigation;

6) patients whose life expectancy is less than the length of follow-up proposed in the trial; and

7) patients unable or unwilling to sign the informed consent document, or commit to the protocol and follow-up schedule.

4. Pre-Treatment Evaluation

Pre-treatment, intraoperative, and post-treatment tests should be clearly defined. These tests should focus on objective, rather than subjective evaluations, whenever possible. The pre-treatment urological evaluation should rule out by appropriate differential diagnostic measures any significant coexisting disease that might simulate the disease under study.

The baseline information collected should allow for a determination of the patient's eligibility, fully characterize the disease state and any concomitant conditions, allow for stratified analyses at the conclusion of the trial, include information regarding confounding factors or prognostic factors (i.e., influencing variables), and include measures of device effectiveness (i.e., outcome variables). Sponsors may modify the treatment evaluations listed below, if appropriate and acceptable justification is provided. As appropriate, pre-treatment evaluation should include:

a. a complete history and physical examination, including the total duration of the patient's symptoms;

b. uroflowmetry including post void residual urine;

c. cystometry evaluation (including pressure-flow measurements);

d. blood and urine chemistry: e.g., urinalysis, urine cultures, complete blood count (CBC), prostate specific antigen (PSA), blood urea nitrogen (BUN), creatinine, and electrolytes;

e. biopsy (if necessary to rule out malignant condition);

f. disease characterization (e.g., benign prostatic hyperplasia (BPH) - prostate weight, length, etc.; whichever is appropriate);

g. assessment of symptomatology (e.g., AUA symptom index for BPH);

h. cystoscopic examination to document urinary tract pathology;

i. other evaluation aspects specific to the intended use of the urological stent such as potential for damage to affected urological structures assessed by cystoscopy, retrograde urethrogram, or ultrasound with adequate resolution;

j. quality of life assessment, including sexual function, using standard scales (if available), as well as the patient's global assessment of the clinical outcome;

k. fertility assessment, if applicable (two specimens of seminal fluid); and

l. information regarding use of medications.

5. Intraoperative Treatment Evaluations

Intraoperative evaluation should include (if appropriate):

a. any difficulties at implantation;

b. the use of various accessory devices (e.g., insertion tools);

c. whether multiple urethral stents were needed, the specific method of insertion, and an assessment of coverage of the targeted area;

d. any repositioning and removals during implantation, including the methods used;

e. whether there were any terminated insertion attempts; and

f. the incidence of any adverse events.

6. Post-Treatment Evaluation

Post-treatment evaluation should be conducted at 1, 3, 6, and 12 months, and at yearly intervals thereafter until marketing approval (alternative follow-up schedules for stents not implanted permanently may be acceptable). FDA believes that follow-up at 8 to 10 days post-treatment would also be in the patient's best interest and should be considered. Post-treatment adverse events should be completely detailed. Post-treatment evaluation at each follow-up should include (if appropriate for the specific trial):

a. physical examination;

b. uroflowmetry including post void residual urine;

c. cystometry at 6 and 12 months (including pressure-flow measurements);

d. blood and urine chemistry: urinalysis and urine cultures at each visit; CBC, PSA, BUN, creatinine, and electrolytes at 6 and 12 months;

e. biopsy (if clinically indicated);

f. assessment of symptomatology (e.g., AUA symptom index);

g. cystoscopic examination (at 6 and 12 months) to characterize the patient's disease state and to assess the effect of the urethral stent treatment, record the degree of epithelialization, and document conditions such as: hyperplasia, migration, encrustation, mechanical integrity of the urethral stent, pathology of the urinary tract, etc.;

h. other evaluation aspects specific to the intended use of the urological stent such as potential for damage to affected urological structures assessed by cystoscopy, retrograde urethrogram, or ultrasound with adequate resolution;

i. quality of life assessment, including sexual function using standard scales (if available), as well as the patient's global assessment of the clinical outcome;

j. fertility assessment at 6 and 12 months; and

k. information regarding use of medications.

The incidence of adverse events should be assessed and analyzed for duration, severity, method of treatment, and cause (e.g., infection caused by specific type of organism, bleeding after insertion, migration due to patient manipulation of stent, etc.).

Data should be gathered to address concerns such as: disease recurrence, incidence and severity of hyperplasia (e.g., growth within or adjacent to the urethral stent); encrustation or stone formation (including stone type); retreatment rate and type; and pathological tissue changes such as malignant growths. For urethral stents indicated for temporary use, the trial should be designed to gather data to address concerns over the expected duration of use. Additionally, long-term concerns (as discussed above) for these devices will most likely require longer follow-up than the labeled limit of use.

Specific possible complications should be thoroughly evaluated, such as: incontinence (i.e., type, frequency, relationship to other complications,

method of treatment, etc.) and UTI (i.e., systemic or localized, organism causing UTI, the treatment method, etc.).

The following information should be collected for each stent removal procedure: removal reason, time until explant and/or subsequent reimplant, and concomitant conditions that required urethral stent removal. Explanted devices should be assessed for the presence of any growth on the urethral stent surface (i.e., biofilm) prior to and after device surface cleaning.

7. Measures of Success and Safety

Prospectively established success criteria should be based on objective and subjective measures (e.g., symptomatology, direct evaluation of the affected area of the urethra, etc.). These study data should be analyzed and reported to demonstrate which patients improved and, after treatment, are in the normal range for the various parameters measured. The criteria should also demonstrate a clinically significant improvement of the patient's condition.

Claims for symptomatic relief should be based on documented improvement in symptom severity. Claims for reduced obstruction should be based on documented improvement of relevant objective measurements. Claims for reduced need for retreatment of the disease should be based on documented, significant reduction in retreatment rate.

The analysis should stratify the data by the number and percentage of patients who achieved greater than 75% improvement, greater than 50% improvement, and less than 25% improvement for appropriate effectiveness outcome variables. The stated percent improvements should be presented for each combination of appropriate outcome variables as well (e.g., greater than 75% improvement in 2 or more outcome variables).

All adverse events (e.g., device malfunctions and treatment/post-treatment complications) should be reported and stratified to determine potential patient groups that have a higher risk of complications. Case report forms should be structured to allow uniform reporting of all adverse events. Adverse events occurring post-treatment should be reported at each follow-up visit and between follow-up visits, if the event only occurred between follow-up visits. A complete description of each adverse event should be presented which discusses the frequency, severity, duration, and resolution (e.g., no treatment, medications,

surgery, or other intervention required). The cause of any patient death should be reported with appropriate medical terminology and in sufficient detail. A tabular presentation of these data may be useful in this regard. All adverse events should be reported, whether or not they appear related to the treatment.

Incontinence needs to be carefully assessed as an adverse event. Any pre-treatment incontinence should be well characterized at baseline. Methods for assessing incontinence should be clearly defined in the protocol and include objective measures when possible (e.g., pad weight test, visual analog scale). The sponsor should ensure that the type of incontinence is recorded (e.g., post-void dribbling, stress, urge, etc.).

The incidence of any hyperplastic tissue response due to the implant should be carefully and uniformly assessed. Cystoscopic evaluations at each investigational site should be as similar as possible (e.g., type and size of cystoscope used, rate/pressure of irrigation fluid). The case report forms and protocol should allow for uniformity in evaluation (e.g., identify extent, severity, and location of hyperplastic tissue). Reference photographs/drawings are recommended to ensure that the investigators uniformly classify observed hyperplasia.

8. Statistical Concerns

The statistical analyses should validate any assumptions made prior to performing the analysis, discuss the statistical tests conducted, address pooling of patients from different investigational sites, and accurately account for all patients in the clinical trial. The statistical report should:

a. compare all treatment data to the control;

b. include statistical measures;

c. stratify the safety and effectiveness data by relevant pre-treatment patient characteristics and treatment parameters (e.g., device size, number of urethral stents implanted, need for retreatment, use of accessory insertion devices used, etc.);

d. account for all patients at each follow-up period;

e. provide graphical presentation of data and results;

f. provide summary tables for all important parameters (including summary tables presenting the raw data for each patient and cohort analysis);

g. stratify the results according to the investigational site and provide justification for pooling results between investigational sites; and

h. identify the methods and results of study masking (i.e., blinding) verification, if applicable.

9. Device Specific Concerns

Urethral stent placement difficulties encountered should be documented and assessed. Other treatment parameters may be analyzed to determine the effect of intraoperative variables.

The data should support the complete range of device sizes that are proposed for marketing. The data should also be presented and analyzed to allow the evaluation of patients who had multiple treatments or who needed retreatment with another type of therapy (i.e., different device, surgery, drugs, etc.).

10. Other Concerns

All patients who later undergo any other treatment should be reported so that the stent's effectiveness in preventing or delaying the need for further intervention can be determined. Biopsy reports should be submitted for patients who later undergo procedures which remove urethral tissue (e.g., TURP, open prostatectomy, urethroplasty, etc.) to histologically evaluate the stented site. Finally, subjects whose stent is removed should be assessed to determine their ability to safely undergo future urologic procedures, i.e., assess whether the placement and removal of the stent restricts the ability to perform future diagnostic procedures or treatments.

The effects of the device on future fertility should be assessed unless the sponsor plans to specifically exclude patients interested in future fertility. At least two semen analyses should be performed pre- and post-treatment as a gross evaluation of semen quality/quantity. In addition, pre- and post-treatment data should be collected to determine the effect of the urethral stent on erectile ability and sexual function of the patient. Time frames for these analyses should be appropriately justified.

The clinical utility of the urethral stent and treatment regimen should be assessed and established. In order to be judged effective, the study should demonstrate clinically significant results, as well as demonstrate that the device functions in accordance with its design. The clinical data should be reported and analyzed to permit a determination of clinical utility (i.e., that the intervention provides clinically meaningful results to treated patients). Labeling claims will generally be restricted to the patient populations in whom clinical utility has been demonstrated. The issue of clinical utility is discussed further in the blue book memorandum #P91-1, "Clinical Utility and Premarket Approval" (May 3, 1991), obtainable from DSMA.

The analyses should be performed on clearly defined cohorts. For example, an intent-to-treat cohort includes all treated patients and is useful during the safety and adverse events analyses. For effectiveness evaluations, a primary cohort of all patients with complete data at each scheduled follow-up, who met the inclusion/exclusion criteria should be used. Other cohorts may be used, but should be clearly defined.

FDA encourages comments on this draft guidance document, and will consider all scientifically valid alternatives to the preclinical and clinical recommendations stated within. This guidance document will be revised periodically based on comments received and as new technologies develop. All comments should be sent to the following address:

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Office of Device Evaluation (ODE)
Center for Devices and Radiological Health (CDRH)
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It is also recommended that the sponsor of a new investigation contact ULDB early in the development of the clinical protocol and prior to submission of an original IDE application.