DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Ms. Dixie Toolson Sells
Vice President, Regulatory Affairs
BSD Medical Corporation
2188 W 2200 S
Salt Lake City, Utah 84119

NOV 18 2011

Re: H090002
2009-0214
BSD-2000 Hyperthermia System
Filed: May 26, 2009
Amended: August 10, 2009, September 15, 2009, and September 30, 2011
Product Code: LOC

Dear Ms. Toolson Sells:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your humanitarian device exemption (HDE) application for the BSD-2000 Hyperthermia System. This device is indicated for use in conjunction with radiation therapy for the treatment of cervical carcinoma patients who normally would be treated with combined chemotherapy and radiation but are ineligible for chemotherapy due to patient related factors. CDRH is pleased to inform you that your HDE is approved subject to the enclosed "Conditions of Approval." You may begin commercial distribution of the device upon receipt of this letter.

In addition to the postapproval requirements in the enclosure, the conditions of approval include that the BSD-2000 Hyperthermia System labeling include information for patients and health care providers that accurately describes what is known about the risk of pelvic necrosis as a result of hyperthermia combined with radiation therapy, a description of how regional temperature distributions are estimated with the BSD thermometry system, a statement that the standard treatment usually involves the use of a 1300 watt BSD system while the 1800 watt system is reserved for larger patients, and that this treatment is reserved for patients ≥21 years of age.

The postapproval reports must also include information on the post-approval clinical study. This study is being conducted to provide additional evidence of the probable benefit and safety of hyperthermia delivered using the BSD-2000 Hyperthermia System in combination with radiation therapy for the treatment of advanced cervical carcinoma. The patients in this study would normally be treated with combined chemotherapy and radiation therapy but have declined chemotherapy. The design of this study is an open-labeled, uncontrolled registry study that will collect data on all patients treated with the device and who agree to participate in the study over a three-year enrollment period. The primary

objectives are to evaluate the rate of complete response, local tumor control, duration of local tumor control, and to evaluate adverse events including acute and late toxicities associated with hyperthermia and radiation therapy. The secondary objectives are to evaluate overall survival at three years and disease free survival. The protocol and all adverse event reporting will be reviewed and approved by the Institutional Review Board and may be subject to inspection by the Food and Drug Administration.

The sale, distribution, and use of this device are limited to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. In addition, in order to ensure the safe use of the device, FDA has further restricted the device within the meaning of section 520(e) of the act under the authority of section 515(d)(1)(B)(ii) of the act insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

FDA wishes to remind you that failure to comply with any postapproval requirement constitutes a ground for withdrawal of the HDE. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

CDRH will notify the public of its decision to approve your HDE by making available a summary of the safety and probable benefit of the device upon which the approval was based. The information can be found on the FDA CDRH Internet HomePage located at http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/HDEApprovals/ucm161827.htm. Written requests for this information can also be made to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the HDE number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the act.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this HDE submission with copies of all approved labeling in final printed form. The labeling will not routinely be reviewed by FDA staff when HDE applicants include with their submission of the final printed labeling a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment.

Any information to be submitted to FDA regarding this HDE should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above HDE number to facilitate processing:

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center – WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

If you have any questions concerning this approval order, please contact Michael D. O'Hara, Ph.D., at (301) 796-0294.

Sincerely yours,

for Alberto Gutierrez, Ph.D.
Director
Office of *In Vitro* Diagnostic Device
Evaluation and Safety
Center for Devices and Radiological Health

Enclosures

## CONDITIONS OF APPROVAL FOR AN HDE

### I. APPROVED LABELING

As soon as possible and before commercial distribution of the device, the holder of an HDE should submit three copies of the approved labeling in final printed form as an amendment (if submitted prior to HDE approval) or supplement (if submitted after HDE approval) to the HDE. The amendment/supplement should be submitted to the U.S. Food and Drug Administration, Center for Devices and Radiological Health, HDE Document Mail Center – WO66-G609, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002.

### II. ADVERTISEMENTS

Advertisements and other descriptive printed materials issued by the HDE holder or private label distributor with respect to this device should not recommend or imply that the device may be used for any use that is not included in the FDA approved labeling for the device. If the FDA approval order has restricted the sale, distribution and use of the device to prescription use in accordance with 21 CFR 801.109 and specified that this restriction is being imposed in accordance with the provisions of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360j(e)) under the authority of section 515(d)(1)(B)(ii) of the act (21 U.S.C. 360e(d)(1)(B)(ii)), all advertisements and other descriptive printed material issued by the holder or distributor with respect to the device shall include a brief statement of the intended uses of the device and relevant warnings, precautions, side effects, and contraindications.

### III. HDE SUPPLEMENTS

Before making any change affecting the safety or probable benefit of the device, the HDE holder should submit a supplement for review and approval by FDA unless a "Special HDE Supplement" is permitted as described under 21 CFR 814.39(d)(2) or an alternate submission is permitted as described under 21 CFR 814.39(e). All HDE supplements or alternate submissions must comply with the applicable requirements under 21 CFR 814.39 of the Premarket Approval (PMA) regulation and under 21 CFR 814.108 of the Humanitarian Device Exemption regulation. The review timeframe for HDE supplements is 75 days except for those submitted under 21 CFR 814.39(e).

Since all situations which require an HDE supplement cannot be briefly summarized, please consult the HDE regulation for further guidance. The guidance provided below is only for several key instances. In general, an HDE supplement must be submitted:

1) When unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification; or

2) If the device is to be modified, and animal/laboratory or clinical testing is needed to determine if the modified device remains safe and continues to provide probable benefit.

HDE supplements submitted under 21 CFR 814.39(d)(2) "Special HDE Supplement - Changes Being Effected" are limited to the labeling, quality control, and manufacturing process changes as specified under this section of the regulation. This provision allows for the addition of, but not the

replacement of previously approved, quality control specifications and test methods. These changes may be implemented upon acknowledgment by FDA that the submission is being processed as a "Special HDE Supplement - Changes Being Effected." Please note that this acknowledgment is in addition to that issued by the Document Mail Center for all HDE supplements submitted. This procedure is not applicable to changes in device design, composition, specifications, circuitry, software, or energy source.

Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of an HDE supplement before implementation and include the use of a *30-day HDE supplement* or *periodic postapproval report*. FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence to the HDE holder that the alternate submission is permitted for the change. Before this can occur, FDA and the HDE holder must agree upon any needed testing, the testing protocol, the test results, the reporting format, the information to be reported, and the alternate submission to be used.

Please note that unlike the PMA process, a supplement may not be submitted for a new indication for use for a humanitarian use device (HUD). An HDE holder seeking a new indication for use for an HUD approved under the provisions of Subpart H of 21 CFR 814, must obtain a new designation of HUD status for the new indication for use and submit an original HDE application in accordance with §814.104. The application for the new indication for use may incorporate by reference any information or data previously submitted to the agency.

## IV. POSTAPPROVAL RECORD KEEPING REQUIREMENTS

An HDE holder is required to maintain records of the names and addresses of the facilities to which the HUD has been shipped, correspondence with reviewing institutional review boards (IRBs), as well as any other information requested by a reviewing IRB or FDA.

## V. POSTAPPROVAL REPORTING REQUIREMENTS

Continued approval of the HDE is contingent upon the submission of postapproval reports required under 21 CFR 814.84 and 21 CFR 814.126.

### A. ANNUAL REPORT

Annual reports should be submitted at intervals of 1 year from the date of approval of the original HDE. Reports for supplements approved under the original HDE should be included in the next and subsequent periodic reports for the original HDE unless otherwise specified in the approval order for the HDE supplement. Three copies identified as "Annual Report" and bearing the applicable HDE reference number are to be submitted to the U.S. Food and Drug Administration, Center for Devices and Radiological Health, HDE Document Mail Center – WO66-G609, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002. Reports should indicate the beginning and ending date of the period covered by the report and include the following information required by 21 CFR 814.126(b)(1):

1. An update of the information required under §814.102(a) in a separately bound volume;

2. An update of the information required under §814.104(b)(2), (b)(3), and (b)(5);

3. The number of devices that have been shipped or sold and, if the number shipped or sold exceeds 4,000, an explanation and estimate of the number of devices used per patient. If a single device is used on multiple patients, an estimate of the number of patients treated or diagnosed using the device together with an explanation of the basis for the estimate;

4. Information describing the applicant's clinical experience with the device. This shall include safety information that is known or reasonably should be known to the applicant, a summary of medical device reports made pursuant to 21 CFR 803, any data generated from postmarketing studies, and information (whether published or unpublished) that is known or reasonably expected to be known by the applicant that may affect an evaluation of the safety of the device or that may affect the statement of contraindications, warnings, precautions, and adverse reactions in the device labeling; and

5. A summary of any changes made to the device in accordance with supplements submitted under §814.108 and any changes required to be reported to FDA under §814.39(b).

B. **ADVERSE REACTION AND DEVICE DEFECT REPORTING**

As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and probable benefit of the device, the holder shall submit three copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the to the U.S. Food and Drug Administration, Center for Devices and Radiological Health, HDE Document Mail Center – WO66-G609, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002. Such reports should be submitted within 10 days after the HDE holder receives or has knowledge of information concerning:

(1) A mixup of the device or its labeling with another article.

(2) Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and

(a) has not been addressed by the device's labeling or

(b) has been addressed by the device's labeling, but is occurring with unexpected severity or frequency.

(3) Any significant chemical, physical or other change or deterioration in the device or any failure of the device to meet the specifications established in the approved HDE that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the HDE holder's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the firm. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the holder shall be

included in the "Annual Report" described under "Postapproval Reports" above unless otherwise specified in the conditions of approval for this HDE. This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of occurrence for each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the HDE holder when determined by FDA to be necessary to provide continued reasonable assurance of the safety and probable benefit of the device for its intended use.

C. **REPORTING UNDER THE MEDICAL DEVICE REPORTING REGULATION**

You are reminded that many FDA requirements govern the manufacture, distribution, and marketing of devices. For example, in accordance with the Medical Device Reporting (MDR) regulation, 21 CFR 803.50 and 21 CFR 803.52, you are required to report adverse events for this device. Manufacturers of medical devices, including in vitro diagnostic devices, are required to report to FDA no later than 30 calendar days after the day they receive or otherwise becomes aware of information, from any source, that reasonably suggests that one of their marketed devices:

1. May have caused or contributed to a death or serious injury; or

2. Has malfunctioned and such device or similar device marketed by the manufacturer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Additional information on MDR, including how, when, and where to report, is available at www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm.

# Deep Hyperthermia and Radiation in the Treatment of Advanced Cervical Carcinoma Patients who would Normally be treated with Combined Chemotherapy and Radiation but are Ineligible for Chemotherapy Due to Patient Related Factors

## I. Study Summary Information

### A. Study Information

This study is being conducted to provide additional evidence of the probable benefit and the safety of the use of hyperthermia delivered using the BSD-2000 Hyperthermia System in conjunction with radiation therapy in the treatment of advanced cervical carcinoma patients who are ineligible to undergo chemotherapy.

### B. Sponsor

BSD Medical Corporation
2188 W 2200 S
SLC, UT 84119
801-972-5555 Ext. 215

### C. Study Title

Deep Hyperthermia and Radiation in the Treatment of Advanced Cervical Carcinoma Patients who are Ineligible for Chemotherapy

### D. Brief Summary

The BSD-2000 Hyperthermia System has received a Humanitarian Use Device (HUD) approval from the US Food and Drug Administration (FDA) for use in the treatment of cervical carcinoma patients who are ineligible for chemotherapy. An HUD approval means that there are limited clinical data that suggest benefit from device use and these data show that the probable benefit to health outweighs the risk of injury or illness from its use. This registry study is being conducted to provide additional evidence of the probable benefit and the safety of the use of hyperthermia delivered using the BSD-2000 Hyperthermia System in conjunction with radiation therapy in the treatment of advanced cervical carcinoma patients who are ineligible to undergo chemotherapy.

This is a Registry Study designed to provide additional evidence of the probable benefit and the safety of the use of the BSD-2000 in conjunction with radiation therapy in the treatment of advanced cervical carcinoma patients who are ineligible to undergo chemotherapy.

### E. Study Type

Interventional; Open Label; Uncontrolled; Registry

**F. Condition**

Advanced Cervical Carcinoma Patients Who Are Ineligible For Chemotherapy

**G. Intervention Type**

Hyperthermia and Radiotherapy

**H. Inclusion Criteria**

- **Patients that elected not to receive chemotherapy**
- Stage IIB or higher cervical carcinoma who are unable to undergo chemotherapy under the following criteria:
    - Inadequate bone marrow function: WBC < 3000/mm3 and platelets < 100,000 mm3;
    - Inadequate renal function: Creatinine > 1.5 mg/dl (urinary diversion is permitted to improve renal function);
    - Inadequate liver function: Bilirubin > 1.5 mg/dl, ALT ≥ 2 x normal, unable to correct serum calcium to a normal level;
    - Systemic disease, or other condition, that, in the opinion of the treating physician, is a contraindication to chemotherapy, including significant coronary artery disease or malnutrition;
    - Significant side-effects from chemotherapy that prevent its use, such as severe nausea or vomiting uncontrolled by standard medical therapy, or known allergy to the chemotherapeutic agents contemplated for use.
- Willing and able to provide informed consent to participate in the registry study.

**I. Exclusion criteria**

- Patients who have implanted, worn or carried medical devices, including cardiac pacemakers, implanted defibrillators, infusion pumps, insulin pumps, cardiac monitoring electrodes and devices, deep brain stimulators, cochlear implants, radiofrequency identification devices attached to devices, or any other implanted active electronic device or monitoring system;
- A body diameter >49 cm from left to right;
- Severe dysfunction of the heart or lungs;
- Severe pulmonary disease with a forced expiratory volume (FEV) <50%;
- **Patients who cannot adequately respond to pain (those with significant neuropathies);**
- Known decrease in circulation in the heated area produced by any means (i.e., vasoconstrictive drugs, DIC, ischemia or other cause);
- Patients who have electrically conductive, metal, or foreign objects in or on or attached to their body;
- Unstable angina pectoris (under medication) with imminent threat of an infarction;

- Myocardial infarction <6 months ago;
- Cardiac decompensation necessitating medication;
- Arrhythmia necessitating medication;
- Heart rate >90bpm;
- Hypertension: diastolic >100 mmHg and/or systolic >180 mmHg, while using medication;
- Hypotension: diastolic <50 mmHg and / or systolic <90 mmHg;
- **Patients who have had prior irradiation to the treatment site;**
- Severe cerebrovascular disease: multiple cerebrovascular accidents (CVA) or a CVA <6 months before treatment;
- Inability to place either an intratumoral or an intraluminal temperature sensor for monitoring of tumor indicative temperatures.

### J. Gender and Age limits

Females; Minimum age of 21 Years; No maximum age limit

## II. Protocol

### A. Treatment

Standard of care radiation therapy (external beam or brachytherapy) plus deep hyperthermia delivered by the BSD-2000, in accordance with this device's instructions for use.

### B. Study Objectives

The BSD-2000 Hyperthermia System has received a Humanitarian Use Device (HUD) approval from the US Food and Drug Administration (FDA) for use in the treatment of cervical carcinoma patients who are ineligible for chemotherapy. An HUD approval means that there are limited clinical data that suggest benefit of device use and these data show that the probable benefit to health outweighs the risk of injury or illness from its use.

This is a Registry Study designed to provide additional evidence of the probable benefit and the safety of the use of the BSD-2000 in conjunction with radiation therapy in the treatment of advanced cervical carcinoma patients who are ineligible to undergo chemotherapy.

The primary objectives are to:

- Evaluate the rate of Complete Response ("CR"), defined as the disappearance of all viable tumor in the irradiated volume;
- Evaluate local tumor control and duration of local tumor control;
- Evaluate adverse events, including acute and late toxicity associated with hyperthermia and radiotherapy treatment.

The secondary objectives are to:

- Evaluate overall survival (defined as death from any cause) at 3 years.
- Evaluate disease free survival.

## C. Study Duration

The estimated time for the study is up to 36 months for subject entry and follow-up.

## D. Inclusion Criteria

- **Patients that elected not to receive chemotherapy**
- Stage IIB or higher cervical carcinoma who are unable to undergo chemotherapy under the following criteria:
  - Inadequate bone marrow function: WBC < 3000/mm3 and platelets < 100,000 mm3;
  - Inadequate renal function: Creatinine > 1.5 mg/dl (urinary diversion is permitted to improve renal function);
  - Inadequate liver function: Bilirubin > 1.5 mg/dl, ALT ≥ 2 x normal, unable to correct serum calcium to a normal level;
  - Systemic disease, or other condition, that, in the opinion of the treating physician, is a contraindication to chemotherapy, including significant coronary artery disease or malnutrition;
  - Significant side-effects from chemotherapy that prevent its use, such as severe nausea or vomiting uncontrolled by standard medical therapy, or known allergy to the chemotherapeutic agents contemplated for use.
- Willing and able to provide informed consent to participate in the registry study.

## E. Exclusion Criteria

- Patients who have implanted, worn or carried medical devices, including cardiac pacemakers, implanted defibrillators, infusion pumps, insulin pumps, cardiac monitoring electrodes and devices, deep brain stimulators, cochlear implants, radiofrequency identification devices attached to devices, or any other implanted active electronic device or monitoring system;
- A body diameter >49 cm from left to right;
- Severe dysfunction of the heart or lungs;
- Severe pulmonary disease with a forced expiratory volume (FEV) <50%;
- **Patients who cannot adequately respond to pain (those with significant neuropathies);**
- Known decrease in circulation in the heated area produced by any means (i.e., vasoconstrictive drugs, DIC, ischemia or other cause);

- Patients who have electrically conductive, metal, or foreign objects in or on or attached to their body;
- Unstable angina pectoris (under medication) with imminent threat of an infarction;
- Myocardial infarction <6 months ago;
- Cardiac decompensation necessitating medication;
- Arrhythmia necessitating medication;
- Heart rate >90bpm;
- Hypertension: diastolic >100 mmHg and/or systolic >180 mmHg, while using medication;
- Hypotension: diastolic <50 mmHg and / or systolic <90 mmHg;
- Severe cerebrovascular disease: multiple cerebrovascular accidents (CVA) or a CVA <6 months before treatment;
- Inability to place either an intratumoral or an intraluminal temperature sensor for monitoring of tumor indicative temperatures;
- **Patients who have had prior irradiation to the treatment site.**

## F. Measurement of Effect

*Toxicity*

An adverse effect related to the subject treatment during or following that treatment. Intended therapeutic effects on the targeted tissue are expressly excluded from this definition.

- Acute toxicity - defined as occurring during the course of treatment or no later than 14 days following completion of the course of treatment.
- Chronic or late toxicity - defined as occurring more than 14 days after completion of the course of treatment.

***Anticipated Adverse Events from Hyperthermia***

The following adverse events (AEs) are expected events that may occur during the course of the hyperthermia treatment. All incidences should be recorded on the case report form (CRF).

- Pain that is treatment limiting;
- Redness, tenderness, burns or blisters on the skin that is exposed to the device;
- Subdermal burn that can result in fat or muscle necrosis or induration;
- Infection/ulceration, usually caused by tumor necrosis;
- Infection/ulceration caused by catheter toxicity;
- Increased heart rate/tachycardia;
- Increase or drop in blood pressure;
- Nausea/vomiting;
- Fever;
- Necrosis/damage to non-target tissues;

- Edema;
- Inflammation;
- Osteonecrosis;
- Nerve impairment, including peripheral neuropathy, numbness, or cramping;
- Mucitis/edema/dermatitis;
- Diarrhea;
- Dysuria, spasms, hematuria;
- Tumor growth along the thermometry catheter track;
- Heat stroke is a rare possibility;
- Ulcer;
- Fatigue.

***Anticipated Adverse Events from Radiation Therapy***

The following adverse events (AEs) are expected events that may occur during the course of the radiation treatment. All incidences should be recorded on the case report form (CRF).

- Necrosis/damage to non-target tissues;
- Diarrhea/altered bowel and/or bladder function;
- Nausea/vomiting;
- Dysuria, spasms, hematuria;
- Mucitis/edema/dermatitis/severe or painful erythema;
- Infertility;
- Hair loss at treatment site (sometimes permanent);
- Dryness of the salivary glands, tear glands, sweat glands, and vaginal mucosa/thickened saliva/difficulty swallowing/change in taste;
- Earaches, sore jaw;
- Cough, shortness of breath;
- Digestive problems;
- Sexual dysfunction;
- Organ damage (including problems with liver, heart, lungs and kidneys);
- Inflammation;
- Ulcers;
- Bleeding;
- Vaginal stenosis;
- Premature menopause;
- Damage to the urinary or gastrointestinal systems;
- Late secondary cancers;
- Fibrosis;
- Fatigue.

Any severe unanticipated device effects should be recorded on the CRF and immediately reported to BSD Medical.

All deaths that occur at anytime during the course of the study should be recorded in the CRF and reported to BSD, regardless of their expectedness.

***Patient Assessments***

Follow-up examinations will be performed at 3, 6, 12, 18, 24, and 36 month intervals. The intervals to first relapse, development of acute or late/chronic complications, including damage to non-target tissue (if assessment is available), disease free survival and overall survival will be recorded. All follow-up reports should include:

- Tumor response, if tumor is evaluable, will be recorded.
- Any adverse events, as determined by clinician, will be detailed on the CRF.
- The current status of any adverse events that occurred at a previous follow-up will be detailed on the CRF.
- Cause of death will be obtained whenever possible and included in the subject's record when available.

***Response Parameters***

Objective response will be determined using standard of care physical examination, laboratory and imaging data available to the treating physician.

- Complete response is defined as absence of tumor in the irradiated volume.
- Partial response is defined as $\geq$50% volumetric regression.
- No response is defined as < 50% volumetric regression with <25% volumetric increase.
- Progressive disease is defined as >25% volumetric increase.
- Tumor control means no growth of the tumor in the irradiated volume (after partial response (PR) or CR) for the indicated period of time; *e.g.*, 6, 12, and 18 months.

Survival will be determined from day 0 of treatment course and will be designated either as overall survival (defined as time to death from any cause) or disease free survival.

## G. Data Collection

Updated data will be submitted to BSD Medical as soon as possible following treatment for all subjects treated. Follow-up information should be sent to BSD Medical every 3 months for the first 6 months of the study, and then every 6 months for 2 years, followed by a final 3 year visit or until the death of the subject.

## H. Subject Identifiers

Sites will be required to use specific subject identifiers in order to adequately track subjects and maintain subject confidentiality.

Each site will be assigned a 2 digit site number specific to the study. Subjects will be assigned a sequential 2 subject number based on the study enrollment. The 2 sets of

numbers will be combined with a dash to form the subject "number". For example, 01 will be the first site involved in the study and the first subject they enroll would be 01, making that subject's number 01-01. The second subject enrolled at that site will be 01-02 and so forth. The next site that enters into the study will be assigned a site specific number of 02. The first subject will therefore be 02-01, the second 02-02, etc.

In addition to the number, the first 2 characters of the subject's last name and the first two characters of the subject's first name will be combined to form a subject "name". Therefore, John Smith would be identified as SMJO.

A complete subject identifier will be the combined number and name. As an example, a subject named Sam Jones who was enrolled at Site 02 as their first subject would have the following identifier, 02-01 JOSA.

## I. Case Report Forms

CRFs will be supplied by BSD Medical Corporation. All CRFs are to be completed either by typing or in legible handwriting using ***blue ink***.

All requested information must be entered on the CRFs. If an item is not available or is not applicable, this fact should be indicated; do not leave a space blank. A correction should be made by striking through the incorrect entry with a single line and by entering the correct information adjacent to it. The correction must be initialed and dated by one of the Investigators or a designated qualified individual. The completed original CRF packets, data updates, and follow-up data are to be sent to BSD Medical as soon as practical after completion.

For subjects treated on this protocol, follow-up will continue until study completion or until subject is lost to follow-up. These data will be recorded on Case Report Follow-Up Forms and sent to BSD as soon as practical after completion.

## J. Study Design

### *Study Endpoints*

The first primary endpoint of the study is a complete tumor response (CR) among subjects who receive hyperthermia and radiation treatment. A complete response is defined as tumor absence in the irradiated volume. CR will be determined using standard of care physical examination, and laboratory and imaging data available to the treating physician.

The second primary endpoint of this study is safety, including adverse events and late toxicity.

The secondary endpoint is survival. Survival will be determined from day 0 of treatment course and will be designated either as disease free or with disease.

## K. Sample Size Requirements

Data will be collected on all patients who are treated with the device and agree to participate in the study during the 3-year enrollment period.

## L. Statistical Methods

***Primary and Secondary Analysis Plan***

This active surveillance study will assess pertinent outcomes and adverse events of advanced cervical cancer patients over a period of 36 months post subject entry. Tumor response and duration, survival status, adverse events, number of study participants, and number of study participants lost to follow-up will be reported.

Data obtained from the CRF at baseline and each follow-up visit will be used to describe outcomes and adverse events over time. All outcomes during the observational period will be evaluated. Presenting tumor status will be evaluated against CR or not a CR as the binary endpoint using logistical regression analysis to determine the covariates that are most predictive of a CR, depending on the available number of participants. The CR primary outcome variable will be determined using the proportion of subjects who have a complete tumor response.

The primary study endpoints are CR, and duration of CR, and findings will be summarized by the proportion of subjects with CR, including 95% confidence intervals.

The secondary study endpoint of acute and chronic/late toxicity will be summarized, showing the proportion by each outcome, including 95% confidence intervals.

The secondary endpoint of survival (overall and disease free) will be summarized by the proportion of subjects, including the duration since day 0 of treatment, that are designated as no disease or alive with disease.

***Overall Analysis Plan***

Frequency tables will be used to show the number of study participants by age and clinical variables, including stage, histology, tumor response and duration of tumor response, nodal involvement, metastases, and adverse events. Descriptive statistics will be used to summarize and compare pre-treatment to post-treatment outcomes for each follow-up time period. Descriptive statistics may include means, standard deviations medians, and ranges. Categorical variables will be summarized using frequencies and percentages, including 95% confidence intervals. Data will be compared to the company's pivotal study data.

***Safety Analysis Plan***

Adverse events will be assessed at each follow-up visit and event rates and 95% confidence intervals will be summarized.

Adverse events will be tracked using a line list. The list will include patient ID, age, type of adverse event(s), classification (acute or chronic/late), and the probable cause of adverse event (radiation or HT). Incidences of adverse event by type of event will be described. Data will be presented as a table showing adverse event(s) by clinical variables, date of follow-up, acute or chronic/late event, and the assessment if adverse event associated with radiation, hyperthermia, or both radiation and hyperthermia.

## M. Study Timeline

- Reporting requirements

  - Interim reports will be submitted to FDA annually following study initiation;
  - A final report will be submitted to FDA 78 months following study initiation.

- Estimated Study Objectives

  - Expected date of study initiation is 3 months following receipt of final HDE approval;
  - Expected (approximate) number of subjects to be enrolled is 1 per month;
  - Expected date of study completion is 36 months following study initiation;
  - Expected date of study follow-up completion is 72 months following study initiation.

# APPENDIX 1

## REGULATORY COMPLIANCE AND STUDY MONITORING

### A. Experimental Plans – Execution

1. Estimated Timetable

The estimated study time period is 3 years.

2. Source Documents

Personnel are required to audit 20% of the CRFs of subjects in this study against original hospital, clinical or office medical records (including laboratory reports and case reports, informed consent, etc.) for accuracy and completeness. The ability to audit the original source documents is a requirement for study participation.

3. Data Reporting

The investigator should provide BSD Medical Corporation with updated data every 3 months for the first 6 months of the study, and then every 6 months for 2 years, followed by a final 3 year visit or until the death of the subject.

4. Adverse Event Reporting

a. Clinical evidence of side effects or toxicity shall be recorded, if and as they appear, on CRFs.

b. If there is no clinical evidence of side effects or toxicity, this also shall be noted.

c. Any unusual, potentially serious or unusually severe adverse events, whether related to treatment or not in the opinion of the Investigator, must be reported immediately to BSD Medical Corporation by telephone and confirmed in writing within 5 (five) working days in all cases and reported immediately to the Institutional Review Board (IRB). BSD Medical Corporation will provide a section on adverse reaction reporting in the CRFs.

## B. Study Monitoring

1. Monitoring and Checking Controls

   a. The Clinical Study Monitor is a representative of the Sponsor. Therefore, the Clinical Monitor may visit the Investigator and the study facility, in addition to maintaining telephone and letter communication. Site visits will include a review of records and source documents for some patients.

   b. A Monitor's on-site visit will be performed as often as required by the Sponsor during the study.

   c. In addition, study data may be subject to inspection by the Food and Drug Administration (FDA).

2. Case Report Forms (CRFs)

   a. CRFs will be supplied by BSD Medical Corporation.

## C. Regulatory Compliance

1. Informed Consent

Before enrollment into the study, each prospective candidate will be given a full explanation of the study. The information that is given to the subject or the subject's representative shall be in language understandable to the subject or the subject's representative. The Informed Consent Form will be prepared by the Investigator and submitted for approval by the Institutional Review Board ("IRB") that is responsible for review and approval of this study. Each Consent Form must include all of the relevant elements currently required by the FDA Regulations, as well as the applicable elements required by the Health Insurance Portability and Accountability Act (HIPAA).

Once the essential information has been provided to the subject and the Investigator assures himself/herself that an individual candidate understands the implications of participating in this study, the subject will be asked to give his/her consent to participation by signing an Informed Consent Form. A copy of the blank form will be provided to BSD Medical. Subjects who cannot give informed consent (i.e., below the legal age or mentally incompetent) are ineligible for this study.

2. Institutional Review Board

This protocol and the Informed Consent Form, prior to initiation of the study, will be submitted to and approved by the IRB. Documentation of this must be received by BSD Medical Corporation before the study can begin. The written approval of the study under review must include the name of the investigational therapy study and/or protocol number, as well as some written indication that the Informed

Consent Form was approved by the IRB and is the same form to be used for this study. Yearly progress reports on the study must be provided to the IRB, and a copy of these progress reports must be sent to BSD. A yearly written renewal of IRB approval must also be submitted to BSD Medical.

3. Adherence to Protocol

Except for an emergency situation in which proper care for the protection, safety and well being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol. Any deviation from the protocol must be recorded and explained, and reported to the IRB.

4. Amendment to Protocol

Should amendments to the protocol be required, the written amendment must be reviewed and approved by BSD Medical Corporation and submitted to the IRB at the Investigator's facility for information and/or approval. If necessary, BSD will formally submit the amendment to FDA for approval.

It should be further noted that where any amendment to the protocol substantially alters the study design or the potential risks to the subject his or her consent to continue participation should again be obtained.

5. Monitoring of the Study

The Clinical Study Monitor, as a representative of the Sponsor, has the obligation to follow this study closely. In so doing, the Clinical Study Monitor will visit the Investigator and the study facility regularly in addition to maintaining necessary telephone and letter communication. Site visits will include a review of records and source documents.

# APPENDIX 2

## HUMAN CONSENT FORM FOR THE ADMINISTRATION OF DEEP HYPERTHERMIA USING THE BSD-2000 IN CONJUNCTION WITH RADIATION

### Treatment

The BSD-2000 Hyperthermia System has received a Humanitarian Use Device (HUD) approval from the US Food and Drug Administration (FDA) for use in the treatment of cervical carcinoma patients who are ineligible for chemotherapy. An HUD approval means that there are limited clinical data that suggest benefit of device use and these data show that the probable benefit to health outweighs the risk of injury or illness from its use. However, the data did not prove that there was any benefit from adding hyperthermia to radiation treatment. This registry study is being conducted to provide additional evidence of the probable benefit and the safety of the use of the BSD-2000 in conjunction with radiation therapy in the treatment of advanced cervical cancer patients who are unable to undergo chemotherapy.

Hyperthermia means "elevated or increased temperature". During a hyperthermia treatment, the cancerous tumor is heated up to a temperature between 40 and 45°C (104 -113° F) for a period of time. Unlike healthy cells, cancer cells cannot tolerate these high temperatures. Thus, some cancer cells will be killed by the heat. The healthy tissue is usually not damaged.

Hyperthermia is used in combination with standard radiation treatment. Hyperthermia potentially can make radiation treatment more effective. Hyperthermia is a "local" treatment, meaning the treatment only works on the targeted local tumor. Hyperthermia treatments, like radiation therapy, involve physicians, physicists, and technicians. You should discuss the details of your radiation treatments, and how your radiation treatments will be coordinated with the hyperthermia treatment, with your radiation oncologist.

Hyperthermia treatments are applied according to your physician's direction. The scheduling of the treatments depends on your radiation therapy schedule. Your physician will give you a hyperthermia treatment schedule before treatments begin.

Heat will be delivered by external RF/microwave energy directed into the tumor by the BSD-2000 and Sigma-60, a cylindrical applicator that will surround the treatment region, and will be given in conjunction with radiation.

Hyperthermia kills some cancer cells by raising the tumor temperature to a "high fever" range, similar to the way the body uses fever naturally when fighting other forms of disease. Raising the tumor to a higher temperature also makes the cancer cells more likely to be killed by the radiation therapy and makes the tumor less able to recover from the effects of the radiation therapy. Thus, hyperthermia is a radiation sensitizer, which means it increases the effect of radiation. The addition of hyperthermia to radiation treatment is not expected to increase the side effects of the radiation therapy because the body is cooled by blood flow. For instance, when your hand or face gets hot, it turns red because the blood rushes to cool it down. This is the body's natural method for cooling down body parts. However, the blood flow in cancer

tissue is slower than normal tissue. This makes the cancer tissue vulnerable to increased heating, even though the healthy tissue is not.

The hyperthermia machine is computer operated and sits in a small room sectioned off from the computer. The room prevents the energy from leaving the room. A physician, technician or a nurse will be watching you from outside or inside the treatment room and can talk to you throughout the treatment. You will be connected to a vital signs monitor and your blood pressure and pulse rate will be taken frequently throughout the treatment.

Other medications may be prescribed before the treatment. Painkillers or tranquilizers may be used in your treatments as long as they do not significantly decrease your awareness of pain sensation in treatment area.

The expected duration of your participation in this study will be approximately 2 to 6 weeks for treatment and approximately 3 years for biannual follow-up visits and evaluation. Follow-up visits and evaluation could extend up to 5 years following treatment. It is very important to be able to monitor the temperature of various parts of your body, as well as of your tumor itself. The following information concerns the pre-treatment and the treatment procedures.

**Patient Authorization**

I hereby authorize Dr. _____ and/or such assistants as may be selected by him/her for use now or at a later time, to perform upon me the following procedures in connection with study on hyperthermia. I understand that the following may be done:

**Catheters**

During the hyperthermia treatment, the tissue is heated to a temperature between 40 and 45°C (104-113° F). The amount of energy needed differs from person to person, so the temperature during the hyperthermia treatments may be measured in several places in my body using temperature sensors. Temperature sensors are placed using catheters. A catheter is a small plastic tube that may be inserted inside your body, into body openings, for example, the vagina, rectum, bladder, or placed into the tumor tissue or on the skin. Thus, you may have catheters placed prior to your treatment.

In some cases, the catheters will be placed inside tumor tissue. Before the start of the series of hyperthermia treatments, the hyperthermia physician will determine whether it is possible to place a catheter directly into the tumor tissue. Placement of the catheter depends on the location of the tumor. It is not always necessary to have the sensor inside the tumor. Your physician will tell you if you will need to have a temperature sensor inserted directly into the tumor. If you don't have a sensor inside the tumor, you will have a sensor inserted into the vagina. These sensors are used to monitor the heating.

The catheter placement will be done under local anesthesia if a catheter is placed inside the tumor tissue. This procedure may be painful for a moment as the local anesthetic is injected, but the pain should subside quickly after the catheter is inserted. You may be given antibiotics prior

to the catheter insertion to prevent infection. The catheters are usually removed after the hyperthermia treatment is completed. Thus, repeat catheter placement is sometimes necessary.

Catheters can be removed quickly and painlessly if they cause discomfort. If a catheter is removed during treatment, another catheter will not be placed in that location and the hyperthermia treatment will continue. At a later hyperthermia session, your physician may decide to use a different catheter placement.

During treatment, a catheter may also be placed under your tongue every 30 minutes to monitor the temperature of your body.

**Potential Benefits**

I understand that the possible benefits associated with the procedures described above include tumor shrinkage or disappearance, relief of symptoms, and/or an improved quality of life. I acknowledge that no guarantee or assurance has been made to me regarding the results, if any, which may be obtained since results cannot be foreseen. Although this therapy has the potential to produce beneficial results, it may be of no benefit to me and may have injurious effects.

I understand there is no guarantee that the tumor will decrease in size or be cured. The physician(s) will take every precaution consistent with good medical practice to ensure that my treatment with this program may prove to be a benefit to me and to the advancement of medical knowledge.

**Side Effects**

I understand that certain hazards and discomforts might be associated with the procedures described above. These could include: pain and discomfort, fatigue, burns/blisters, ulceration, and infection. Additional side effects such as nausea, fever, nerve impairment, and painful urination from insertion of a catheter into the bladder have been observed in some hyperthermia treatments. Other side effects may include redness, tenderness or even small blisters on the skin that is located directly in the machine. Some patients have experienced burns that are under the skin that resulted in some fat or muscle tissue death or hardening. A few patients have experienced increased heart rate, inflammation, fluid retention, increase or decrease in blood pressure, nausea/vomiting, tumor growth along the catheter insertion site, and bowel and/or urinary incontinence lasting more than 1 month and only partly recovering following treatment. You may experience a change in bowel activity, including diarrhea, loose stool, or frequency of bowel movements. Possible side effects that were NOT experienced during the clinical study of the BSD-2000 system could include damage to non-target organs, possibly including fistula (an abnormal urine passage between the urethra and rectum), worsening of pre-existing disease, increased drug activity, and thermal stress. The therapy's effect on fertility is unknown.

Although precautions have been taken, heat stroke is a rare possibility.

Although no serious damage to the normal organs has been observed in clinical studies, it is possible that some damage to normal tissues could occur.

It is not expected that hyperthermia will alter the side effects of radiation with the exception of the possibility of enhanced tissue reaction in the vicinity of the heated area; however, there may be unexpected or enhanced side effects from the combined treatment.

I understand that certain hazards and discomforts are also associated with the radiation treatment I will receive and these hazards and discomforts have been discussed with me.

Should any of the above side effects appear, my physician(s) have assured me that they will take adequate steps to reduce or eliminate these effects by whatever means are necessary, of which there can be no assurance that such effects can be reduced or eliminated.

## Alternate Treatments

If the treatment does not control the tumor, it may be possible to still use other treatments. Please discuss possible treatments with your physician.

## Contraindications

Your physician will consider many factors before recommending the BSD-2000 treatment for you. There are certain conditions that make a person ineligible for hyperthermia. Hyperthermia contraindications (indications against use) are listed below. BSD-2000 therapy should not be used for a patient with any of these conditions. For these patients, the risks are greater than the potential benefits.

### Decreased Pain Response

Because a patient's ability to feel pain is an essential safety factor for hyperthermia treatment, hyperthermia is contraindicated in patients whose pain response has been significantly reduced by any means (such as significant neuropathies, previous surgery or radiation therapy, regional or general anesthetic, or other conditions).

### Decreased Circulation

Since excessive heating of normal tissue is prevented by normal blood flow, it is important that adequate blood flow be present and maintained in all normal tissues located near the heating field. Hyperthermia should not be used on patients with reduced blood circulation, which may be caused by vasoconstrictive drugs (which restrict the blood vessels), disseminated intravascular coagulation (a blood clotting disorder), ischemia (an insufficient supply of blood to an organ), or other medical condition.

### Active or Metal Implants

Hyperthermia should not be used on patients with pacemakers, metal implants (for example, hip or knee replacements), or other active medical devices that are implanted, worn or carried, including, implanted defibrillators, infusion pumps, insulin pumps, cardiac monitoring electrodes and devices, deep brain stimulators, cochlear implants, or any other implanted active electronic device or monitoring system because hyperthermia may interfere with the operation of the active

medical device and the metal implant may heat more quickly and to a higher temperature than other tissue.

Weak Heart or Lungs

Hyperthermia may cause an increase in pulse and/or blood pressure, similar to an aerobic exercise workout. Thus, hyperthermia should not be used for patients with unstable angina, arrhythmia that requires medication, significantly elevated heart rate or blood pressure, significantly reduced blood pressure, a heart attack or a stroke within the last 6 months, or significant pulmonary disease that requires supplemental oxygen.

Other contraindications include a body diameter >49 cm from left to right, prior irradiation to the treatment site, the inability to place a temperature sensor for monitoring of tumor indicative temperatures, or patients who are less than 21 years of age.

**Confidentiality of Individual Health Information**

I agree to allow my pre-existing and newly created individual health information, including my name, medical records, treatment information, and pathologic materials, to be made available to the members of the medical staff of the hospital/clinic and to other authorized individuals, including employees and representatives of BSD Medical Corporation, the Sponsor of this clinical research study, in order for them to evaluate the results of this treatment. I understand the disclosure of this information will continue until this clinical research study is closed or until information is no longer required by FDA regulations, requirements, or orders. I understand study data may be subject to review and investigation by FDA. I understand that the confidentiality of my records will be maintained in accordance with applicable state and federal laws and that all reasonable precautions will be taken to maintain the confidentiality of my medical records. I understand I may inspect a copy of my information. I understand I may refuse to sign this authorization to allow availability of my individual health information to the individuals specified above without jeopardizing treatment, except for research related treatment, including participation in this clinical study. I understand I can revoke this authorization at any time.

**Financial Remuneration**

The researchers involved with this study will receive no payments from BSD, the study Sponsor, either directly or indirectly, for conducting this research.

**Questions**

I understand the investigator is willing to answer any inquiries that I may have concerning the procedure herein described. All the inquiries I have at this time have been answered.

**Participation**

I understand that my participation in this research study is voluntary and that I may refuse to participate and/or withdraw my consent and discontinue participation in the project or activity at

any time without penalty, loss of benefits, to which I am otherwise entitled, or penalty or prejudice in my future treatment. I also understand that I may ask a question or state a concern to the University's Chairman of the Human Studies Committee and that the investigator will, on request, tell me how to reach the Committee Chairman.

I also understand that the physician can terminate my participation without my consent at any time in the event of physical injury or other condition that makes further treatment an unnecessary risk in the medical opinion of my physician.

**Pregnancy**

To the best of my knowledge I am not pregnant, and if I do become pregnant I will notify the principal investigator of my pregnancy. If it is possible that I may be pregnant and not know it, I agree to have a pregnancy test performed.

**Physical Injury**

I have been informed that in the event of physical injury resulting from this research procedure immediate first aid treatment will be provided and payment for this care will be paid by me and/or my insurance company.

Financial compensation is not available for this treatment or in the event of physical injury resulting from this research project. In the event of physical injury to me as a result of my participation in this treatment program, I may contact _____, Patient Representative, at_____, extension _____, for information and required forms.

**Agreement**

The physician(s) involved in this treatment is _____ _____. His/her address is _____ _____. He/she may be contacted by telephone at _____ if I should have any questions regarding my treatment.

I have discussed the above material with my physician(s) and they have answered my questions concerning the treatment program and other methods available for treatment of my disease. I have reviewed the foregoing statements and understand them. I understand that I am not required to enter this treatment program and that if I agree to participate it will be a voluntary decision. I know how to contact my physician and his/her staff regarding any questions or problems.

I am of sound mind and clearly understand the risks involved in the use of hyperthermia and hyperthermia equipment.

The representation contained in this human consent form shall be binding upon assigns, successors, heirs and legal representatives of the undersigned and shall inure to the benefit of you and your successors and assigns. Any and all warranties expressed or implied are expressly disclaimed.

I have received a copy of this informed consent, which I have read and understood. I hereby consent to the performance of the above procedures on me.

PATIENT_____ DATE __/__/__

WITNESS_____ DATE __/__/__

NOTE: If there is anything in the foregoing material you do not understand, ask the doctor to explain it before you sign.

**Physician's Statement**

I have provided a verbal explanation of the treatment program herein outlined, along with a copy of this consent form. I have encouraged the patient to request additional information and have discussed possible alternative forms of treatment.

PHYSICIAN _____

Emergency telephone number _____

# APPENDIX 3

# CASE REPORT FORM

List the 2 first initials from the last name and first name (Sample - John Doe: DO - JO) Last Name ☐☐ - First Name ☐☐ Patient ID # _____ Institution or Institution #: _____

# Deep Hyperthermia and Radiotherapy in the Treatment of Advanced Cervical Carcinoma Patients who are Ineligible for Chemotherapy

## PRETREATMENT EVALUATION

| | |
|---|---|
| AGE: _____ (at time of treatment) | DATE OF BIRTH: MO / DAY / YR |
| PHYSICIAN: (PRINT) | |
| PHYSICIAN SIGNATURE: | DATE FORM COMPLETED: MO / DAY / YR |

PRIMARY TUMOR HISTOLOGY: ADENOMCARCIMOMA ○ SQUAMOUS CELL CARCINOMA ○ OTHER ○ _____

STAGE: II B ○ III ○ IVA ○ IVB ○

NODAL STATUS: NO ○ N1 ○ N2 ○

TUMOR EXTENSION NEAR THE PELVIC WALL: YES ○ NO ○

METASTASES: YES ○ NO ○ SITES: 1 _____ 2 _____ 3 _____

MAXIMUM TUMOR DIAMETER IN HYPERTHERMIA TREATMENT FIELD: _____

HYPERTHERMIA TREATMENT SITE INCLUDES ALL KNOWN TUMOR: YES ○ NO ○

*List the 2 first initials from the last name and first name (Sample - John Doe: DO - JO)* Last Name First Name ☐☐-☐☐ Patient ID # _____ Institution or Institution #: _____

## CURRENT THERAPY

TOTAL RADIATION DOSE DELIVERED TO TREATMENT SITE: Gy_____

EXTERNAL BEAM DOSE: Gy_____ BRACHYTHERAPY DOSE: Gy_____

### HYPERTHERMIA TREATMENTS

**Sigma 60** (Number of Treatments):

**Sigma 60 Elipse** (Number of Treatments):

**Total Number of Treatments:**

**Treatment Start Date:** MO / DAY / YR

**Treatment End Date:** MO / DAY / YR

**Therapeutic Temperature:** (For All Treatments): Minimum _____ Maximum _____ Average (over time) _____

**TOTAL THERAPEUTIC TIME** (minutes at ≥40°C):

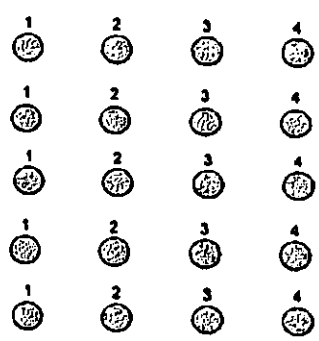
**OVERALL PATIENT TOLERANCE**

1 2 3 4 5 6

1 No patient complaints.
2 Complaints of patient concerning increased temperature, cold sensation or enclosed environment, which could be relieved by counseling and sedatives. There is no interruption of hyperthermia.
3 Frequent and more severe complaints, leading to reduction of applied power, but all sessions being completed.
4 Increasing complaints which necessitate discontinuing at least one treatment session but with subsequent completion of other hyperthermia sessions.
5 Severe complaints by patient not associated with patient or disease condition demanding discontinuation of hyperthermia on a permanent basis.
6 Treatment terminated or interrupted due to patient or disease condition.*

***If course of therapy was discontinued prior to completion, explain reason for termination in detail:***

**TEMPERATURE SENSOR/PROBE LOCATION**




1 - Tumor - Interstitial
2 - Tumor - Intraluminal
3 - Oral
4 - Normal Tissue/Surface
5 - Other (specify) _____

**NOTES:**

## BSD-2000 HYPERTHERMIA SYSTEM REGISTRY STUDY

*List the 2 first initials from the last name and first name (Sample - John Doe: DO - JO)* Last Name ☐☐ - First Name ☐☐ Patient ID # _____ Institution or Institution #: _____

## END OF TREATMENT EVALUATION ≤14 WEEKS FOLLOWING TREATMENT

MAXIMUM TUMOR DIAMETER IN HYPERTHERMIA TREATMENT FIELD, IF AVAILABLE: _____

TUMOR RESPONSE IN HYPERTHERMIA TREATMENT FIELD: ○ Complete Regression (100%) ○ Partial Regression (~50%) ○ Minimal Regression (~01%-50%) ○ Zero Regression (0%) ○ Progressive Disease ○ Not Evaluable ○ Not Available

| ADVERSE EFFECTS REACTIONS TO TREATMENT (Describe in detail under COMMENTS all items with an asterisk) | | MEDICAL TREATMENT OF ADVERSE EFFECT REQUIRED? | ADVERSE EFFECT STATUS (1 Resolved, 2 Improved, 3 No Change, 4 Worse) |
|---|---|---|---|
| **Pain** Yes ○ No ○ | Caused by: Hyperthermia-Treatment Limiting ○ Hyperthermia-Non-Treatment Limiting ○ Pre-existing Condition ○ Patient or Disease Condition ○ | Yes* ○ No ○ | 1 ○ 2 ○ 3 ○ 4 ○ |
| **Burn/Blister** Yes ○ No ○ Size in cm: _____ | Caused by: Surface ○ YES* ○ NO ○ Fat Necrosis ○ YES* ○ NO ○ Muscle Necrosis ○ YES* ○ NO ○ | Yes* ○ No ○ | 1 ○ 2 ○ 3 ○ 4 ○ |
| **Infection** Yes ○ No ○ | Caused by: Tumor Necrosis ○ Normal Tissue ○ Pre-existing ○ Catheter ○ Unknown ○ Other* ○ | Yes* ○ No ○ | 1 ○ 2 ○ 3 ○ 4 ○ |
| **Ulceration** Yes ○ No ○ Size in cm: _____ | Caused by: Tumor Necrosis ○ Normal Tissue Reaction* ○ Pre-existing Condition ○ Unknown ○ Other ○ | Yes* ○ No ○ | 1 ○ 2 ○ 3 ○ 4 ○ |
| **Systemic Stress** Yes ○ No ○ | Caused by: Treatment Limiting* ○ Non-Treatment Limiting ○ | Yes* ○ No ○ | 1 ○ 2 ○ 3 ○ 4 ○ |
| **Nerve Impairment** Yes* ○ No ○ **Nerve Impairment Symptoms:** Peripheral Neuropathy YES* ○ NO ○ Numbness YES* ○ NO ○ Cramping YES* ○ NO ○ Other* YES* ○ NO ○ | Caused by: Radiotherapy ○ Hyperthermia ○ | Yes* ○ No ○ | 1 ○ 2 ○ 3 ○ 4 ○ |

OTHER REACTION* Yes ○ No ○ Describe: _____

NECROSIS/DAMAGE TO NON-TARGET TISSUE Yes* ○ No ○

NOT EVALUABLE Yes ○ No ○

*COMMENTS: Specify and describe adverse effects and any medical treatments necessary to provide clinical management of adverse effects. Explain any adverse effect status of 'worse'. Explain pre-existing contributory conditions. Add any comments regarding treatment.*

_____

_____

_____

_____

_____

ADVERSE EFFECTS:

NOT RELATED TO HYPERTHERMIA: ○

UNLIKELY RELATED TO HYPERTHERMIA: ○

POSSIBLY RELATED TO HYPERTHERMIA: ○

PROBABLY RELATED TO HYPERTHERMIA: ○

DEFINITELY RELATED TO HYPERTHERMIA: ○

## BSD-2000 HYPERTHERMIA SYSTEM REGISTRY STUDY

*List the 2 first initials from the last name and first name (Sample - John Doe: DO - JO)* Last Name ☐☐ - First Name ☐☐ Patient ID # _____ Institution or Institution #: _____

# PATIENT AND TUMOR STATUS - FOLLOW-UP

DATE OF OBSERVATION

FOLLOW-UP OBTAINED FOR THE FOLLOWING:133 ○ 3 MO. FU ○ 6 MO. FU ○ 12 MO. FU ○ 18 MO. FU ○ 24 MO. FU ○ 36 MO. FU ○ OTHER (Specify) _____

### PATIENT STATUS

ALIVE ○ DEAD ○

ANY TREATMENT TO STUDY SITE FOLLOWING HYPERTHERMIA?: YES* ○ NO ○

*IF YES, EXPLAIN IN COMMENTS SECTION BELOW:

### TUMOR STATUS

EVALUABLE ○ *Complete tumor status section below. UNEVALUABLE* ○ *Explain in comments section.

EVIDENCE OF DISEASE Yes ○ No ○

TUMOR IN HYPERTHERMIA TREATMENT FIELD Yes ○ No ○

IF YES, TUMOR CONTROLLED IN HYPERTHERMIA TREATMENT FIELD? Yes ○ No ○ If yes, state how long in months: _____

MAXIMUM TUMOR DIAMETER IN HYPERTHERMIA TREATMENT FIELD: _____

TUMOR OUT OF HYPERTHERMIA TREATMENT FIELD Yes ○ No ○

TUMOR RESPONSE IN HYPERTHERMIA TREATMENT FIELD: ○ *Complete Regression (100%)* ○ *Partial Regression (>50%)* ○ *Minimal Regression (>0%<50%)* ○ *Zero Regression (0%)* ○ *Progressive Disease* ○ *Not Evaluable* ○ *Not Available*

### ADVERSE EFFECTS REACTIONS TO TREATMENT (Describe in detail under COMMENTS all items with an asterisk)

| | MEDICAL TREATMENT OF ADVERSE EFFECT REQUIRED? | ADVERSE EFFECT STATUS (1 Resolved, 2 Improved, 3 No Change, 4 Worse) |
|---|---|---|
| ARE THERE ANY HYPERTHERMIA RELATED ADVERSE EFFECTS PREVIOUSLY REPORTED ON THE CRF THAT ARE UNRESOLVED: Yes* ○ No ○ | YES* ○ NO ○ | 1 ○ 2 ○ 3* ○ 4* ○ |
| HYPERTHERMIA RELATED CHRONIC/LATE ADVERSE EFFECT (>14 DAYS FOLLOWING TREATMENT) NOT PREVIOUSLY REPORTED ON CRF: YES* ○ NO ○ (If yes, specify below) | | |
| Necrosis/Damage to Non-Target Tissue* ○ Nerve Impairment* ○ Other* ○ _____ | YES* ○ NO ○ | 1 ○ 2 ○ 3 ○ 4* ○ |

*COMMENTS: *List any treatment to study site following hyperthermia. Provide explanation of an unevaluable tumor status. Explain any adverse effect status of 'worse' or 'no change' and any late adverse effects from hyperthermia treatment.*

**ADVERSE EFFECTS:**

NOT RELATED TO HYPERTHERMIA: ○

UNLIKELY RELATED TO HYPERTHERMIA: ○

POSSIBLY RELATED TO HYPERTHERMIA: ○

PROBABLY RELATED TO HYPERTHERMIA: ○

DEFINITELY RELATED TO HYPERTHERMIA: ○

List the 2 first initials from the last name and first name (Sample - John Doe: DO - JO) Last Name ☐☐ - First Name ☐☐ Patient ID # _____ Institution or Institution #: _____

# END OF STUDY - FINAL PATIENT STATUS REPORT

*End of Study Assessment/Final Study Status must be completed for all patients.*

**END OF STUDY PATIENT STATUS:**

COMPLETED ○ REMOVED ○ WITHDRAWN ○

**DATE PATIENT COMPLETED, REMOVED OR WITHDREW FROM STUDY:** MO / DAY / YR

*If Patient Removed or Withdrawn, specify reason below.*

**SPECIFY BELOW PRIMARY REASON PATIENT WAS REMOVED OR WITHDRAWN FROM STUDY:**

- ○ PATIENT REQUEST OTHER THAN ADVERSE EVENT (SPECIFY REASON)
- ○ ADVERSE EVENT *Please specify adverse event and explain in space provided below.
- ○ PATIENT DEATH DATE OF DEATH: MO / DAY / YR.
  CAUSE OF DEATH: _____
- ○ PATIENT DID NOT COMPLETE SCHEDULED FOLLOW-UP *Please explain in space provided below.
- ○ PATIENT RELOCATED
- ○ OTHER *Please explain in space provided below.

**ANY UNRESOLVED ADVERSE EFFECTS AT TIME OF EXIT FROM STUDY?** YES ○ NO ○

*If YES, Please explain in space provided below.

***COMMENTS AND EXPLANATIONS:**

DATE FORM COMPLETED: MO / DAY / YR

SIGNATURE OF INDIVIDUAL ADMINISTERING FORM: