SUMMARY OF SAFETY AND PROBABLE BENEFIT

I. GENERAL INFORMATION

Device Generic Name:	Hyperthermia System
Device Trade Name:	BSD-2000 Hyperthermia System
Applicant's Name and Address:	BSD Medical Corporation 2188 W 2200 S Salt Lake City, UT 84093
HDE Number:	H090002
HUD Number:	09-0214
Date of HUD Designation:	May 15, 2009
Date of Panel Recommendation:	This HDE was not presented to the Radiological Devices Advisory Committee.
Date of GMP Inspection:	February 21-28, 2011
Date of Notice of Approval to Applicant	November 18, 2011

II. INDICATIONS FOR USE

The BSD-2000 Hyperthermia System is intended for use in conjunction with radiation therapy for the treatment of cervical carcinoma patients who would normally be treated with combined chemotherapy and radiation but ineligible for chemotherapy due to patient related factors.

III. CONTRAINDICATIONS

- 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);
- Patients who have had prior irradiation to the treatment site;

- Patients who are less than 21 years of age;
- 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.

IV. RESTRICTIONS

The sale, distribution, and use of the BSD-2000 Hyperthermia System are restricted to prescription use. The BSD-2000 Hyperthermia System is to be used only by qualified operators upon the prescription and under the supervision of a physician who is experienced in clinical hyperthermia.

V. WARNINGS and PRECAUTIONS

The WARNINGS and PRECAUTIONS can be found in the BSD-2000 Hyperthermia System labeling.

VI. DEVICE DESCRIPTION

The BSD-2000 Hyperthermia System delivers localized therapeutic heating (hyperthermia) to solid tumors by applying radiofrequency (RF) energy at the frequency range of 75 to 120 MHz. The BSD-2000 delivers energy to a patient using a power source and an array of multiple antennae that surround the patient's body. The BSD-2000 System creates a regional or localized electromagnetic (EM) field within the tissues of the body, which produces localized heating. Localized heating is caused by ionic or electric conduction and molecular rotational friction absorption, which produces heating that is dependent on temperature and frequency. The BSD-2000 creates a cylindrically convergent radiated wavefront that utilizes the principles of constructive and destructive interference to create a central focusing of energy. Thus, the energy delivered by the BSD-2000 can be electronically focused to produce a localized power field, which can be adjusted to target the 3-dimensional shape, size, and location of the tumor, thus providing dynamic control of the heating delivered to the tumor region. This method of therapeutic heating utilizes the adjustment of frequency, phase, and amplitude from multiple power

sources, along with applicator selection and patient positioning, to optimize the deposition of heating energy into the targeted body tissues.

The BSD-2000 consists of four major subsystems: an RF power generator delivery subsystem; a proprietary, thermistor-based, thermometry subsystem; a computerized monitoring and control subsystem; and an applicator subsystem that includes an applicator and patient support system; as well as various accessories, including a tissue equivalent Quality Assurance lamp phantom that provides verification of the energy focus, pattern steering, and system operations.

The BSD-2000 comes in two configurations, a lower power basic system (BSD-2000B) that has a maximum power output of 1300 watts and an upgraded higher power system (BSD-2000U) that has a maximum power output of 1800 watts. The system includes a deep-heating Sigma Base and applicators that are used inside of an enclosed RF shielded treatment area (not supplied by BSD Medical Corporation) in order to comply with FCC regulations.

VII. ALTERNATIVE PRACTICES AND PROCEDURES

Three alternative cancer treatment methods are currently available to treat cervical cancer: surgery, radiation therapy, and chemotherapy. Some treatment approaches utilize two or more of these methods in combination. In addition, biological therapy is sometimes used for cancer treatment.

VIII. MARKETING HISTORY

The BSD-2000 System has been commercially marketed internationally since 1988. The BSD-2000 System is available in China, Germany, the Netherlands, Norway, Italy, Austria, and Switzerland. The device had not been withdrawn from any market due to any reason related to the safety or effectiveness of the device.

IX. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Potential adverse effects associated with deep hyperthermia include:

- Pain
- Blistering
- Burns
- Ulceration
- Catheter toxicity
- Fat or muscle necrosis
- Induration
- Exacerbation of pre-existing disease
- Enhanced pharmacological activity of certain drugs
- Thermal stress
- Change in bowel function

X. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

Scientific Validation of the BSD-2000

System and subsystem tests were performed on the BSD-2000 to validate equipment design and performance; to verify operational safety, reliability, and ease of use; and to characterize the RF energy deposition within tissue and the stray field emissions of the device. SAR is defined as the rate of energy absoption per unit mass (W/kg), and determination of SAR provides a scientific method for characterizing the therapeutic dose for a hyperthermia system. SAR testing data were in agreement with heating patterns generated from both 2D and 3D pretreatment planning programs and with heating data from patient magnetic resonance images taken during a hyperthermia treatment with the BSD-2000. The data demonstrated that the BSD-2000 heating pattern can be controlled and steered, validating the design parameters of the system and the energy focus capabilities of the BSD-2000.

Conformance to Performance Standards

The BSD-2000 complies with applicable performance, consensus, and industry recognized standards, including:

- ***Medical Electrical Equipment Safety and EMC/EMI Standards***
  - IEC 60601-1-2 Class A (2001-09)
  - EN 55011 (1998) Class A
  - IEC 61000-3-2 Harmonic Emissions (2000-03)
  - IEC 61000-3-3 Flicker (2002-03)
  - EN 60601-1, Incl. A1, A2, and A3 (Safety)
- ***Risk Management***
  - ***ISO 14971:2000***
  - ***ISO 13485:2003***
- ***Software Design and Validation***
  - ANSI/AAMI/IEC 62304:2006 Standard
  - ISO 14971
  - IEC 60601-1-4

Additional Bench Testing

- Verification and Validation of Energy Focus;
- Verification and Validation of the Heating Parameters;
- Hyperthermia Equipment Testing;
- Predicted Reliability and Durability;
- Human Factors Design;
- Sterility;
- Shelf-Life for BSD-2000;
- Useful or Expected Life and Reuse Life.

B. Animal Studies

A single animal study was conducted by Erasmus Medical Center – Daniel den Hoed Cancer Center (DHCC), Rotterdam, The Netherlands, prior to initiation of the pivotal Phase III clinical study. The protocol was approved by the Erasmus Medical Center Intuitional Animal Care and Use Committee. The results demonstrated that an adequate increase of temperatures could be achieved in the center of the pelvis, without significantly increasing the superficial tissue temperatures. The steering of the focus resulted in a change of the temperature distribution that was in agreement with the predicted steered temperature distribution. There was no evidence of "hot spots" outside of the target volume and no side effects were recorded.

XI. SUMMARY OF CLINICAL STUDIES

A. Pivotal Phase III Study

1. Study Design

A Phase III, prospective, randomized study was conducted at Erasmus Medical Center – Daniel den Hoed Cancer Center (DHCC), Rotterdam, The Netherlands, from May 1990, to September 1996. The study was conducted to compare hyperthermia (HT) and radiation (RT) to radiation only treatment of locally advanced tumors of the cervix, bladder, and rectum. The primary endpoints of the study were local control and duration of local control, and duration of local palliation. Secondary endpoints were acute toxicity, late toxicity, disease free survival and total survival. A total of 65 patients were in the advanced cervical cancer subgroup. Of these 65 patients, 33 were randomized into radiotherapy combined with hyperthermia and 32 patients were randomized into radiotherapy alone.

2. Patient Assessment

Patients and Randomization. Advanced cervical patients were eligible for the trial if they required standard RT for cervical cancer International Federation of Gynecology and Obstetrics (FIGO) Stages IIB, IIIB, or IVA. Patients

needed to have a World Health Organization (WHO) performance status less than 2 and expected survival greater than 6 months. Absolute contraindications for a treatment with hyperthermia were a pacemaker, hip replacements or other metal implants with a dimension >10 cm, a body with a diameter >49 cm, and/or severe dysfunction of the heart or lungs.

Radiotherapy and Hyperthermia Treatment. Radiotherapy was given per published international standards. Hyperthermia was given once weekly, 4 hours after radiotherapy, to a maximum of 5 treatments. The patients were given Zanex 30 minutes prior to the treatment. The treatment objective was hyperthermia treatment for 60 minutes after interstitially measured tumor temperature had reached a minimum of 42°C, or for a maximum total duration of 90 minutes. A maximum induction period of 30 minutes was used to increase the tumor to intratumoral temperatures greater than 42°C. Treatment delivery settings were adjusted depending on observed temperatures and feedback from the patients. When temperatures of 42°C were reached in one or more locations inside the tumor, or after 30 minutes, the 60-minute hyperthermia treatment period began. The temperature elevation for normal tissues was limited to 43°C, with the exception of subcutaneous fat tissue situated >1 cm from the skin, where 44°C was acceptable.

Response Definition. Complete response was defined as disappearance of all viable tumors in the irradiated volume. Duration of pelvic tumor control was defined as either the time between the date of randomization and date of local progression within the irradiated volume or death from toxicity. Secondary end points were overall survival and toxic effects from RT or HT. Overall survival was defined as the time between randomization and death or lost follow-up. Late toxicity (effects occurring ≥3 months after the last RT) was scored using the radiation morbidity scoring criteria of the Radiation Therapy Oncology Group and European Organization for Research and Treatment of Cancer (RTOG/EORTC).

3. Demographic Data

Patient Population. There were 65 advanced cervical patients referred to as the BSD Intent-to-Treat ("BSD ITT") population. Of the 65 patients in the BSD ITT population, 33 were randomized into RT + HT and 32 patients were randomized into RT alone.

Eighty-two percent (82%) of patients had FIGO Stage IIIB or IVA tumor, 70% had positive pelvic lymph nodes on CT scan, and tumor diameter was 6 cm or larger in 65%. Almost all cervical tumors were irresectable. No patients with cervical tumors had metastases present. Few patients (<10%) with cervical tumors had surgery prior to treatment. Their median age was 53 years, a large portion of patients had pathologically enlarged lymph

nodes, and those patients with a FIGO stage IIB tumor all had tumor extension near the pelvic sidewall, all prognostic indicators that are associated with a poorer outcome for cervical cancer. The distribution of prognostic factors was balanced equally over the two treatment groups.

Eligibility for chemotherapy was not specifically assessed as part of patient demographics. However, given that renal failure and poor physical condition are often considered contraindications to chemotherapy, it is reasonable to assume that many DHCC study patients would not qualify for chemotherapy. Specifically, due to the pattern of local extension of cervical cancer and the advanced state of the disease in many study patients, it is likely that many study subjects would have urethral obstruction and secondary renal failure that would have constituted a contraindication to chemotherapy.

Baseline Data. The subjects included in this analysis included 65 ITT BSD-2000 subjects. The randomization was well balanced with 33 HT + RT subjects and 32 RT subjects.

Table 1 summarizes the baseline parameters for the BSD ITT population. In general, all of the characteristics appeared similarly distributed between the treatment arms.

Table 1. Baseline Summary, BSD ITT Population (n=65)

Parameter	Category or Statistic	Cervical RT	Cervical RT+HT
Sex n(%)	F	32 (100%)	33 (100%)
	M	0	0
Age (yr)	N	32	33
	Mean±SD	53.3±13.0	53.2±13.2
	Median	50.5	55.0
	Min,Max	30,82	29,75
WHO Performance Score n(%)	0	27 (84%)	25 (76%)
	1	5 (16%)	8 (24%)
	2	0	0
	3	0	0
Hemoglobin Category n(%)	LE 7	10 (36%)	9 (32%)
	GT 7	18 (64%)	19 (68%)
Tumor Stage n(%)	Irresectable	30 (94%)	32 (97%)
	Recurrent	2 (6%)	1 (3%)
Tumor Stage n(%)	Missing	0	0
	T2	0	0
	T2b-lat	6 (19%)	6 (18%)
	T3	0	0
	T3b	22 (69%)	22 (67%)
	T4	4 (13%)	2 (6%)
	T4a	0	3 (9%)
	T4b	0	0
Maximum Tumor Diameter n(%)	Missing	0	0
	<=60mm	11 (34%)	12 (36%)
	60-80mm	11 (34%)	7 (21%)
	>80mm	10 (31%)	14 (42%)
Maximum Tumor Diameter (mm)	N	32	33
	Mean±SD	73.9±23.4	78.7±20.2
	Median	70.0	80.0
	Min,Max	30,150	45,130
Tumor Elsewhere at Study Start n(%)	No	32 (100%)	33 (100%)
	Yes	0	0
M Category n(%)	Missing	0	0
	M0=No Metastases Present	32 (100%)	33 (100%)
	M1= Metastases Present	0	0
Nodal Status n(%)	Missing	0	0
	N0	29 (91%)	28 (85%)
	N1	3 (9%)	5 (15%)
	N2	0	0
Year Started Study n(%)	90	0	0
	91	6 (19%)	5 (15%)
	92	6 (19%)	6 (18%)
	93	3 (9%)	4 (12%)
	94	8 (25%)	5 (15%)
	95	6 (19%)	8 (24%)
	96	3 (9%)	5 (15%)
Surgery before Treatment n(%)	Missing	0	1 (3%)
	No	31 (97%)	29 (88%)
	Yes	1 (3%)	3 (9%)

Parameter	Category or Statistic	Cervical RT	Cervical RT+HT
Histology n(%)	Missing	0	0
	Adenocarcinoma	4 (13%)	2 (6%)
	Squamous Cell Carcinoma	27 (84%)	29 (88%)
	Transitional Cell Carcinoma	0	0
	other	1 (3%)	2 (6%)
Grade n(%)	Missing	5 (16%)	6 (18%)
	Good	2 (6%)	2 (6%)
	Moderate	16 (50%)	11 (33%)
	Poor	9 (28%)	13 (39%)
	No Diff.	0	1 (3%)

Treatment Summary. For the BSD ITT population, the median RT dose was about 65.5 Gy for both treatment arms administered over a median of about 50 to 51.5 days for cervical subjects across both treatment arms. One patient in the RT arm received HT therapy (per patient request). The percentage of cervical patients in the RT + HT arm who received less than five sessions of HT was 42% (cervical), though 63% received four or five sessions.

4. Safety Results

There were no unanticipated safety considerations reported from the study. In the BSD ITT Population, 30/33 (91%) of the patients in the RT + HT arm had at least 1 acute adverse event while 28/31 (90%) of the patients in the RT arm did. There was no difference between the RT arm and the RT + HT arm. The side effects were generally self-resolving or managed conservatively.

Table 2: summarizes the number of patients who had any reported acute adverse event in the BSD ITT Population, excluding only 1 patient with all acute adverse event data missing.

Table 2: Any Acute Adverse Event Summary, BSD ITT Population with Adverse Event Information (n=64)

Group	No AE	At Least 1 AE
Cervix RT	3 (10%)	28 (90%)
Cervix RT+HT	3 (9%)	30 (91%)

Table 3: below, summarizes the safety data for the BSD ITT Population. Six (out of 65) patients had less RT than planned, 5/32 (16%) were in the RT arm and 1/33 (3%) were in

the RT + HT arm. One was for general poor condition, 1 was according to plan, and 4 were due to disease progression outside of the treatment volume.

Table 3: Safety Summary, BSD ITT Population (n=65)

Parameter	Category	Cervical RT	Cervical RT+HT
Skin RT effect acute	Missing	2 (6%)	0
	None	8 (25%)	9 (27%)
	Erythema, Dry Desquamation	8 (25%)	11 (33%)
	Severe/Painful Erythema, Some Epidermolysis, Slight Edema	13 (41%)	13 (39%)
	Confluent Epidermolysis also Outside Skin Folds, Pitting Edema	1 (3%)	0
Skin HT effect acute	Missing	32 (100%)	4 (12%)
	None	0	28 (85%)
	Ulceration	0	1 (3%)
Subcutis-HT effect acute	Missing	32 (100%)	4 (12%)
	None	0	26 (79%)
	Induration with Tenderness<24 hr	0	1 (3%)
	Induration with Tenderness 1-7 days	0	1 (3%)
	Induration with Tenderness, Postponement of Subsequent Treatment	0	1 (3%)
Small intestine effect (acute)	Missing	1 (3%)	0