FDANEWS

Drug Industry Daily

Jan. 28, 2010 | Vol. 9 No. 19

DDMAC: Bracco Cited for Website Misrepresentations of Study

Bracco Diagnostics made false and unsubstantiated claims about its drug Isovue and omitted or minimized risks on a website, an FDA untitled letter says.

The Division of Drug Marketing, Advertising and Communications (DDMAC) cited the company for several pages of the website that falsely indicated that a study called IMPACT was a prospective trial comparing the primary endpoint of incidence of contrast-induced nephropathy (CIN) between Isovue (iopamidol) and GE Healthcare's Visipaque (iodixanol-320), which are used in cardiovascular imaging. The web pages have since been taken down, the company said.

The study was actually a post hoc combination of two completed trials that listed CIN risk as a secondary endpoint, the letter says.

The website also makes "numerous comparative claims," based on IMPACT, for which the study doesn't provide substantial evidence or clinical experience, DDMAC says. For example, the website says there is not a statistically significant difference in the rate of CIN between Isovue and Visipaque. IMPACT study authors indicated that a study of about 3,800 cases would be necessary to detect a 50 percent reduction in CIN incidence, the letter says, whereas the IMPACT study only examined 166 patients.

"We respectfully disagree with the FDA," Carlo Medici, president and CEO of Bracco Diagnostics, told *DID*. "In order to maintain good relationships with the agency, we have decided to comply and have taken the website down," he added.

The letter posted recently to the FDA website also cites the company for minimizing and omitting risks. The website does not include Isovue's boxed warning about intrathecal administration, the agency says. The site includes the statement "Please click on the 'downloads & PI' tab for full prescribing information," the letter notes, but that does not mitigate the omission of the warning, the letter says.

The Isovue website also does not present the risk information comparably with safety information, DDMAC says. Web pages labeled "Study Conclusions," "Study Summary" and "Study Design" use large headings and centrally located graphics to highlight the reportedly low risk of CIN in the IMPACT study, but the risk information is given in smaller type without headings. Additionally, the video on the website uses a telescript format for the risk information at the end of the video, with a voiceover spoken at a notably faster pace than the efficacy presentation.

DDMAC asked the company to stop disseminating the materials and provide a written response by Jan. 22. Bracco responded to the letter by the deadline, Medici said, and has stopped using the website.

The letter is available at www.fdanews.com/ext/files/Isovue-Letter.pdf. — Lauren Lentini

300 N. Washington St., Suite 200, Falls Church, VA 22046, USA.
Phone (703) 538-7600 - Fax (703) 538-7676 - Toll free (888) 838-5578.

FDANEWS

Clinical Trials Advisor

Feb. 18, 2010 | Vol. 15 No. 4

CF Investigator Gets Warning for Consent, Protocol Issues

Samya Nasr, an investigator in several clinical cystic fibrosis (CF) trials, received a warning letter for informed consent failures and violations of protocol.

In one CF study, the sponsor required revisions to the original informed consent form approved by the IRB, including the stated purpose of the study. Nasr made changes to the form, but the sponsor still had concerns about the wording, according to the Jan. 28 warning letter posted recently to the FDA website.

The sponsor shipped the study drugs to Nasr on the condition that the consent form be revised and submitted to the IRB for approval again and that subjects already enrolled be re-consented.

Revised Consent Form

The IRB approved the third version of the consent form about six months later. However, the FDA found no documentation during its inspection last summer of the Ann Arbor, Mich., site that the six subjects already enrolled had been informed of the true purpose of the study, as required by the sponsor.

Three of the subjects were not re-consented with the revised form until three months after the IRB had approved it, the agency says.

Nasr responded to this observation on the Form 483 by creating a standard operating procedure (SOP). But the SOP includes no details about the methods the site would take to verify consistency of all elements on the informed consent form, protocol, investigator's brochure and other documentation, according to the letter.

In another CF study, the site collected saliva samples from three subjects for genetic testing even though the patients had not checked a box on the informed consent form permitting it, the letter says.

Nasr told the FDA the error was detected before the genetic analysis was done, but the agency says the error was not identified until its inspection. When the sponsor was informed of the problem during the inspection, it ordered the samples to be destroyed.

The FDA also warned Nasr for not ensuring that the research was conducted according to the investigational plans. For instance, in a study of inhaled denufosol tetrasodium in CF patients, one subject was given a chest X-ray an hour after taking the drug during the second visit, but the protocol indicated an X-ray must be performed at the first visit. The FDA also found that several adverse events in another study were not recorded in the case report form.

Research Changes

A third observation involved failure to report all changes in research to the IRB and making changes without IRB approval.

In one trial, the site distributed tote bags, diary cards and subject calendars that had not been approved by the IRB. Although Nasr was asked in four monitoring letters in 2006 whether the items had been approved, the IRB was not told of the changes until March 2007 — a month before the IRB terminated the study, the letter says.

The FDA approved Nasr's corrective action, which included developing an SOP, training study team members on IRB amendments and reminding them that all items and services given to trial subjects must be approved by the IRB in advance.

"I am in the process of responding to the letter and implementing additional corrective actions to fully address FDA's remaining observations," Nasr told *CTA*.

The warning letter is available at www.fdanews.com/ext/files/WomensHospitalWL.pdf. — Lauren Lentini

300 N. Washington St., Suite 200, Falls Church, VA 22046, USA.
Phone (703) 538-7600 - Fax (703) 538-7676 - Toll free (888) 838-5578.

FDANEWS

Devices & Diagnostics Letter

March 8, 2010 | Vol. 37 No. 10

FDA Cracks Down on Makers of Unapproved Ear Candles

Delivering on a promise it made last month, the FDA has sent warning letters to 15 companies that manufacture or sell ear candles, telling them to stop marketing and distributing unapproved devices.

The letters, posted to the agency's website last week, assert that an ear candle is a device under the Food, Drug and Cosmetic Act because "it is intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease, or is intended to affect the structure or function of the body."

The letters reference claims the companies listed on their websites, including that the candles can remove earwax and yeast, improve hearing and balance, increase circulation, treat allergies, reduce temporomandibular joint syndrome and relieve headaches and tinnitus.

The FDA also conducted inspections at two ear candle manufacturers — Wally's Natural Products and White Egret in Ogden, Utah — and determined that the facilities did not meet good manufacturing practice requirements.

Wally's Auburn, Calif., facility is "spectacularly clean" and the candles it manufactures are "triple-inspected to make sure only the top-quality products go out," manager David Reese told *D&DL*, adding that he isn't worried about passing an FDA inspection. His company does not consider ear candles medical devices.

The FDA posted a patient safety alert on its website last month, saying ear candles may cause serious injury, including perforated eardrums and burns (*D&DL*, Feb. 22). The agency is concerned that the devices are marketed for use with children. — Lauren Lentini

300 N. Washington St., Suite 200, Falls Church, VA 22046, USA.
Phone (703) 538-7600 - Fax (703) 538-7676 - Toll free (888) 838-5578.

FDANEWS

Generic Line

March 3, 2010 | Vol. 27 No. 5

KV Subsidiary Reaches Settlement With Justice, to Pay $25.8 Million

Ethex, a KV Pharmaceutical subsidiary, has agreed to plead guilty to two felony counts and pay $25.8 million in fines and restitution to resolve a Justice Department investigation.

Under the settlement, which is subject to court approval, Ethex will plead guilty to failing to file field alert reports for out-of-specification dextroamphetamine and propafenone tablets in September 2008, KV said last week.

The company recalled several lots of generic drugs in November 2008, including dextroamphetamine and propafenone, because they may contain oversized tablets that could have as much as twice the amount of active ingredient (*Generic Line*, Nov. 12, 2008).

Ethex will pay $2.3 million in restitution to the federal government as part of the $25.8 million fine. It also will pay about $1.8 million to Medicare and Medicaid. In exchange, Justice agrees not to pursue further prosecution, according to a KV SEC filing.

KV entered into a consent decree with the FDA a year ago following a production and shipment hold related to oversized tablets of beta-blocker Toprol (metoprolol succinate) (*Generic Line*, March 4, 2009). KV plans to cease operations at Ethex, but it intends to resume manufacturing of its generic products once the requirements of the consent decree have been met, the company says in the SEC filing.

The settlement would not restrict KV's manufacturing of generic drugs, the company says.

KV did not respond to a request for comment by press time. — Lauren Lentini

300 N. Washington St., Suite 200, Falls Church, VA 22046, USA.
Phone (703) 538-7600 - Fax (703) 538-7676 - Toll free (888) 838-5578.

FDANEWS

Devices & Diagnostics Letter

Feb. 22, 2010 | Vol. 37 No. 8

Court: Manufacturers Not Liable for Physicians' Off-Label Use

The U.S. Court of Appeals for the Ninth Circuit has affirmed a district court summary judgment that DePuy Spine did not promote its Charite artificial disc for off-label use.

The appellate court determined that selling a device to a physician who intends to use it for an off-label purpose is not the same as promoting an off-label use.

The ruling "flies in the face of some of the off-label investigations that are going on currently and have gone on in the past," Mark DeWyngaert, managing director at Huron Consulting Group, told *D&DL*.

For instance, a jury in an Oregon state court recently determined that I-Flow could be held liable for a physician's off-label use of its pain pump with a catheter to administer medication following shoulder surgery (*D&DL*, Feb. 1).

However, the FDA always has held that physicians may use a device as they see fit in treating their patients, DeWyngaert added.

The court acknowledges that while the Federal Food, Drug and Cosmetic Act protects off-label use of devices, it includes regulations prohibiting devicemakers from promoting such uses. "However, a manufacturer is not liable merely because it sells a device with knowledge that the prescribing doctor intends an off-label use," according to the ruling.

The plaintiff, Camille Carson, alleged that DePuy was negligent in promoting off-label use of the Charite disc, a Class III device approved for implant at one level of the spine. Carson's physician implanted discs in two levels of her spine. The physician did not discuss the off-label use with a DePuy representative, but a sales representative was present during Carson's surgery, according to court documents.

The appellate court also upheld the lower court's decision that Carson did not prove her manufacturing defect claim and that DePuy did not violate a federal standard in manufacturing the product.

The U.S. District Court for the Central District of California's judgment in *Camille Carson v. DePuy Spine, Inc.* was filed Sept. 19, 2008. — Lauren Lentini

300 N. Washington St., Suite 200, Falls Church, VA 22046, USA.
Phone (703) 538-7600 - Fax (703) 538-7676 - Toll free (888) 838-5578.

FDANEWS

Devices & Diagnostics Letter

Feb. 8, 2010 | Vol. 37 No. 6

OST Receives Warning Letter for GMP, QS Violations

OST Medical, which manufactures Sentinel enteral feeding pumps, must bring in an independent expert to audit its quality systems (QS), according to a warning letter that cites the company for ongoing systemic violations in its QS and good manufacturing practice (GMP) deviations.

When the independent audit of its manufacturing and quality assurance systems is completed, OST's CEO must review the auditor's report and certify the company has initiated or completed all the recommended corrections, the FDA says. The audit report and CEO's initial certifications must be submitted by July 27 with any subsequent certifications due Jan. 27, 2011, and Jan. 27, 2012.

OST did not establish and maintain procedures to verify and validate corrective and preventive actions (CAPAs), the letter says. One CAPA was verified and closed by someone not employed at OST, and the company was not able to explain this practice during the FDA's Nov. 23 to Dec. 31 inspection of the Warwick, R.I., facility.

The company received two complaints that the labels on the Sentinel pumps were smudging and chipping off, according to the Jan. 27 warning letter posted to the agency's website last week. OST contracted with an unapproved supplier to print the labels and then didn't inspect them to ensure they met specifications, the FDA says.

In other supply issues, the company contracted with a supplier not on its approved supplier list for disposable delivery sets, which it distributes. OST did not have adequate documentation upon receipt to demonstrate that the sets met required specifications, according to the letter. The company failed to inspect three out of four lots of delivery sets from its supplier. The FDA also warns OST for failing to establish and maintain procedures to ensure all received product meets specifications.

The company failed to maintain a device history record that includes adequate acceptance records, and OST did not review, evaluate or investigate complaints involving the possible failure of a device, labeling or packaging to meet specifications, the FDA says in the letter. OST also failed to establish and maintain procedures designating a specific unit to review and evaluate such complaints. Files for six complaints had no documentation of an investigation being conducted before they were closed, according to the letter.

OST did not respond to a request for comment by press time. The warning letter is available at www.fdanews.com/ext/files/OST-Medical-Inc-WL.pdf. — Lauren Lentini

300 N. Washington St., Suite 200, Falls Church, VA 22046, USA.
Phone (703) 538-7600 - Fax (703) 538-7676 - Toll free (888) 838-5578.

FDANEWS

Drug Industry Daily

March 5, 2010 | Vol. 9 No. 44

Takeda's Kapidex Name to Change to Cut Medication Errors

Takeda Pharmaceuticals North America will change the name of its heartburn drug Kapidex to Dexilant to prevent medication errors.

Kapidex (dexlansoprazole) is a proton-pump inhibitor treatment, but there have been reports of confusion with AstraZeneca's Casodex (bicalutamide), used to treat advanced prostate cancer, and Actavis' opioid analgesic Kadian (morphine sulfate), according to the FDA. Takeda will begin marketing the drug as Dexilant in late April.

The FDA approved the name change as part of its Safe Use Initiative, a collaboration between the agency and drugmakers to identify drugs and drug classes associated with significant preventable harm, which was launched last November (*DID,* Nov. 5, 2009).

Dexilant will have a new National Drug Code number, but the formulation, indication and approved dosages will remain the same, the company said Thursday.

Last month, Novartis Consumer Health changed the name of its Maalox Total Relief (bismuth subsalicylate) due to medication errors caused by confusion with Maalox liquid antacid products (*DID,* Feb. 18). — Lauren Lentini

300 N. Washington St., Suite 200, Falls Church, VA 22046, USA.
Phone (703) 538-7600 - Fax (703) 538-7676 - Toll free (888) 838-5578.

FDANEWS

Devices & Diagnostics Letter

March 22, 2010 | Vol. 37 No. 12

Z-Medica Is First Devicemaker to Get FDA Closeout Letter

Z-Medica received the first device closeout letter — three months after it got an FDA warning letter citing validation and complaint-handling issues.

After conducting a second inspection of Z-Medica's Wallingford, Conn., facility and evaluating a Feb. 22 response letter from the company, the FDA concluded Z-Medica's proposed corrective actions would clear up the problems cited in the warning letter.

The agency issued the closeout letter March 1 and posted it to its website last week.

"No one wants to get a warning letter. But with that having happened, getting a rapid closeout letter is probably the best thing a company can do in response," Denny Lo, senior vice president of Z-Medica, told *D&DL*.

To clear up the warning letter quickly, the company did everything it could to address the FDA's concerns. "We tried to do it in a timely fashion and an objective fashion so it can be verified," Lo said.

The Dec. 3 warning letter included four citations related to the company's QuikClot Combat Gauze.

In the letter, the FDA acknowledged the company's November response to a Form 483, but it requested copies of revalidated sterilization data, an approved process-validation procedure, evidence of employee training, and a revised and approved complaint-handling procedure. Z-Medica responded as quickly as possible, Lo said.

The FDA reinspected Z-Medica's facility Jan. 26 through Feb. 2. "They were primarily focused on making sure that what we said we would do was in fact done," Lo said.

The closeout letter process is one of six steps FDA Commissioner Margaret Hamburg announced last August in an effort to tighten the agency's enforcement efforts. Other steps included giving companies only 15 days to respond to Form 483 citations after an inspection and 15 days to respond to a warning letter. The new program went into effect for warning letters issued after Sept. 1 (*D&DL*, Aug. 10, 2009).

While not all types of warning letters are eligible for a closeout letter, Hamburg said she hoped that receiving one would become a "top industry policy," especially in cases of ongoing violations.

Devicemakers expressed concern last month that no closeout letters had been issued yet to a device manufacturer.

Having a closeout letter posted to the FDA's website is critical in demonstrating to customers, investors and international regulatory agencies that a manufacturer is in compliance with FDA regulations, Darin Martin, senior vice president of quality assurance and regulatory affairs for Symmetry Medical, said (*D&DL*, Feb. 1).

As for Z-Medica, getting "the closeout letter so quickly is something we appreciate," Lo said, "because it puts in the public record that we have adequately addressed the observations."

The closeout letter is available at www.fdanews.com/ext/files/Z_Medica_LLC_COL.pdf, and the warning letter is at www.fdanews.com/ext/files/Z_Medica_LLC_WL.pdf. — Lauren Lentini

300 N. Washington St., Suite 200, Falls Church, VA 22046, USA.
Phone (703) 538-7600 - Fax (703) 538-7676 - Toll free (888) 838-5578.