INSIDE PMB
February 2007

GONE FISHIN'

Pharmaceutical Management Branch * Cancer Therapy Evaluation Program * Division of Cancer Treatment and Diagnosis * National Cancer Institute
6130 Executive Blvd * Suite 7149 * Rockville, Maryland 20852 * Phone: (301) 496-5725 * Order fax: (301) 480-4612 * Other fax: (301) 402-0429
*E-mail: pmbafterhours@mail.nih.gov

OUR MASCULINE SIDE: FISHING

After a couple of issues that were a tad bit girlie, the guys on our staff suggested we may need to chose a tougher theme for this issue. The decision: Fishing. We start with this definition from Wikipedia, which the girls find hilarious: "Fishing is the activity of hunting for fish by hooking, trapping, or gathering animals not classifiable as insects which breathe in water or pass their lives in water. By extension, the term fishing is applied to pursuing other aquatic animals such as various types of shellfish, squid, octopus, turtles, frogs, and some edible marine invertebrates. The term fishing is not usually applied to pursuing aquatic mammals such as whales, where the term 'whaling' is more appropriate. Fishing is an ancient and worldwide practice with various techniques and traditions.....modern fishing is both a recreational and professional sport." Hope we don't make too many gaffs...it's sink or swim time at the PMB!

Angling for Info: NCI Drug Information Resources

Since its inception in 2005, the NCI Drug Dictionary (http://www.cancer.gov/drugdictionary) has more than doubled its number of entries from approximately 500 to more than 1,200.

In early October 2006, NCI's Office of Communications launched an online collection of consumer-friendly drug information summaries. The collection compiles information from the Food and Drug Administration, the National Library of Medicine, and the NCI. It covers drug approvals, proper drug use, drug interactions, side effects, clinical trial results, and NCI press releases and news stories. In addition, each summary contains a link to current clinical trials in which the drug is being used. These drug information summaries are available online at http://www.cancer.gov/cancertopics/druginfo/alphalist.

Terminal Tackle: Filling Bottles

Several astute clinicians in the field have noted that for some oral agents, bottles of 30 (for example) don't always contain 30. (Others just attribute patients' claims that there were more or fewer tablets in the bottle than expected as akin to a "fish story.") They report sorafanib and perifosine often have discrepant counts. We trolled for information, and this is what we caught:

•Weight based counters (might they be scales?) are cheaper, easier and less costly to maintain, and more flexible with respect to a variety of dosage forms and sizes.

•Many early development oral agents may be produced at a lower cost by small companies specializing in early development work. Such companies will always have a weight based counter on every line--and perhaps one optical counter.

•Inherent process variability at early development makes it difficult to hit the same dosage mass as later on in development.

•In the case where there may be inaccuracy in loading, most companies will (or at least should) err on the high side to make sure bottles are not underloaded.

•As technology improves, optical counters are becoming less expensive. Many contractors now have both weight and optical counters.

•All open label bevacizumab protocols (NSC 704865) have been amended, making the 400 mg vial available. This size saves a few minnows in the hood each time you make a dose!

•The Captisol diluent that accompanies AZD6244 (NSC 741078) can now be stored at room temperature.

Will my paperwork look fishy to auditors?

Question: A pharmacist (whose initials are NB) writes, "I have auditors coming soon, and one of our DARFS looks terrible. It's a placebo-controlled trial and the staff guessed about what to put in the lot # field--some put one number, some put another. Anyway you get the picture. Our internal compliance officer reviewed and corrected the DARF to maintain consistency, and now it's cross-out city! Can I rewrite the DARF for legibility sake??
Answer: Technically, you cannot rewrite the DARF and dispose of the originals. If it's a safety issue, rewrite the DARF and staple it to the "junky" copy with a note about why you did it. You can't do it just for the halibut!

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Aqueous Solutions

What do you get when you cross a fishing theme with the All-American version of Trivial Pursuit? PMB's adaptation: Aqueous Solutions! Provide the answers to the following questions to earn your six color wedges.

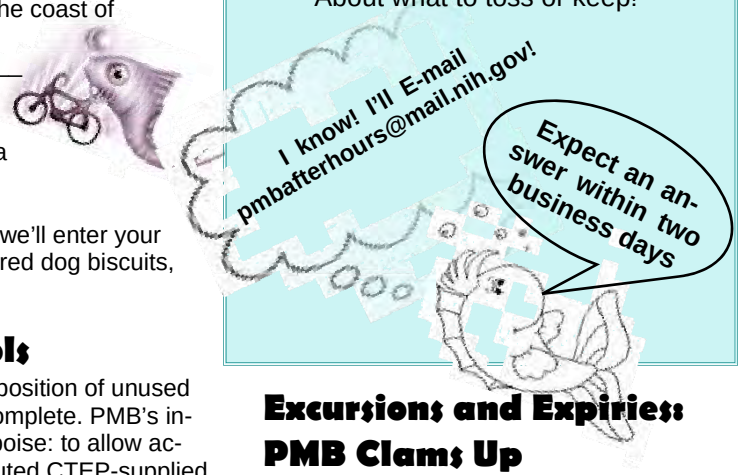
1. Blue: People. Whose team discovered Phorboxazole A in an Indian Ocean sponge off the coast of Western Australia?
   a) that's a made up drug b) Tadeusz Molinski at UC/Davis
   c) Indian Ocean sponges only grow in the Indian Ocean
2. Pink: Entertainment. What problem did participants in trials employing shark cartilage complain about the most?
   a) scaly skin b) the agent's odor! c) bulging eyes
3. Yellow: History. When did the FDA approve the first marine-derived cancer drug, an extract of a Caribbean sea sponge, Cytosar-U®?
   a) June 1969 b) June 1979 c) June 1989
4) Purple: Places. Bryostatin is isolated from *Bugula neritina*, which is an organism that attaches itself to the bottoms of boats off the coast of
   a) Maine b) Alaska c) California
5. Green: Sports and leisure. A _____ needs a _____ like a fish needs a bicycle.
6. Orange: Wild card! *Carpe diem* means
   a) fish of the day b) live in the present c) a fish a day keeps the doctor away

Send your answers to pmbafterhours@mail.nih.gov and we'll enter your name into the quarterly drawing for cookies or tuna-flavored dog biscuits, all homemade!

Phil the Phishy Pharmacist
is having awful trouble,
It's midnight on the ocean floor
and he needs answers on the double!

El Nino warmed his ice chest,
His drugs are at room temp!
He dreams of swimming home to rest
In a hammock made of hemp.

How will he get an answer
When all he needs is sleep?
He needs a knowledge enhancer
About what to toss or keep!



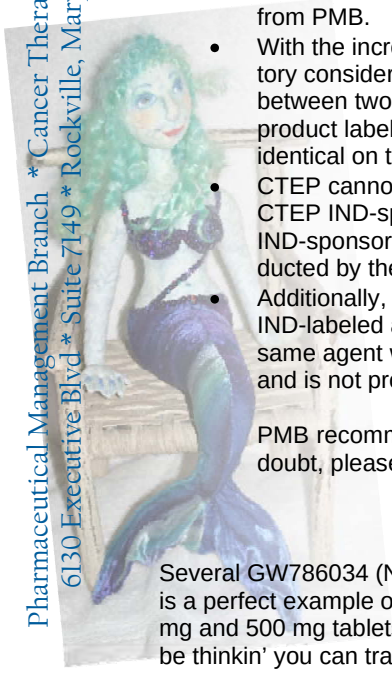
Ferrying Agents Between Protocols

FDA regulations hold IND sponsors accountable for disposition of unused investigational agent supplies after investigations are complete. PMB's investigational agent transfer process has an explicit porpoise: to allow accountability while minimizing waste of previously distributed CTEP-supplied agents. (It's like catching a fish that's too small: You throw it back in.) How? PMB can authorize you to transfer agent from a completed protocol to another CTEP-approved protocol using the same CTEP-supplied agent, formulation and strength.

Although there are circumstances that may allow transfer of an agent from one active trial to another, the transfer mechanism is not intended to be a "back-up" process for the Clinical Drug Request. When you attempt to transfer an agent from one protocol to another because you forgot to order, our sea sirens go off! So transfers are possible, but what's the catch?

- Transfer of agent from an active trial requires prior authorization from PMB.
- With the increasingly complex clinical trial process, other regulatory considerations may also impact the ability to transfer agent between two studies; for example, the IND sponsor of a trial or the product labeling itself (i.e., commercial or investigational) must be identical on the giving and receiving protocols.
- CTEP cannot authorize transfer of a CTEP-supplied agent from a CTEP IND-sponsored trial to a Group IND-sponsored or company IND-sponsored trial or vice-versa, even if the trials are being conducted by the same Cooperative Group.
- Additionally, CTEP cannot authorize transfer of a CTEP-supplied, IND-labeled agent provided under an IND to a protocol using the same agent which is CTEP-supplied, but commercially-labeled and is not provided under an IND.

PMB recommends pre-approval of all transfers. If there is any doubt, please call.



Upstream Dream

Several GW786034 (NSC 737754) protocols will begin accrual soon. This is a perfect example of a transfer complexity: one protocol (7529) uses 100 mg and 500 mg tablets…all other studies use 200 mg and 400 mg. Don't be thinkin' you can transfer the 100 mg tablets to any other protocol!

Excursions and Expiries: PMB Clams Up

If you've had an experience like Phil the Phishy Pharmacist, and you've called or E-mailed because your PMB-distributed agent got too hot or too cold, you may note that our staff will clam up when you ask for a temperature range at which the agent(s) is stable. We must approve each excursion individually. Our support staff cannot and will not float you an E-mail with excursion information; a pharmacist must do that.

And, if you are a provider located in the US, we can no longer give you the retest date for agents we distribute. We will tell you if the agent(s) is expired. Please don't try to worm anything else out of us!

A Fine Kettle of Fish

Please congratulate November's contest winners:

Jeffrey Doi RPh, HonBSc, BScPhm
Clinical Trials Pharmacist
Toronto, Ontario

Dana Kelley, PharmD
IDS Pharmacist
St. Louis, MO

Cyndi Rup
Investigational Pharmacy Technician
Worcester, MA

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Fish or Cut Bait

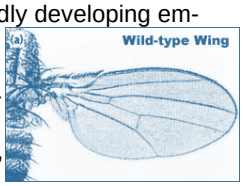
It's a riddle: What's the difference between fish and bait?* In addition to the obvious, invertebrates–like bait (nematodes) and flies–develop cell proliferation abnormalities, but they fall short clinically and pathologically of being recognized as cancer. Cancer, however, is a reality for all vertebrates from the simplest (fish) to what is debatably the most complex (humans). Animal models of cancer thus are preferably vertebrate.

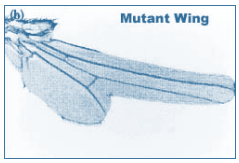
Researchers have found that despite the fact that fish's and humans' last

common ancestor roamed (or bobbed) more than 300 million years ago, their disease biology and histology is quite similar, especially in cancer. Benign and malignant tumors are common in wild fish. A decade ago, rainbow trout were used to demonstrate that aflatoxin contaminants in some foods are powerful carcinogens and a major cause of liver cancer in some developing nations.

Enter the zebrafish, named for the stripes on its side and known scientifically as *Danio rerio.* It can regenerate organs and tissues and is an ideal vertebrate cancer model: inexpensive, easy to work with, and extremely useful for study of human cancers. Most carcinogens affecting humans affect zebrafish and can lead to the same types of cancer. Additionally, zebrafish embryos develop outside the mothers body and are transparent like those of worms and flies, allowing direct observation at early developmental stages. But like mice, zebrafish have vertebrate anatomy, physiology, and tumor biology. And, zebrafish are easier to breed and work with than mice.

When the human genome sequence is compared to the zebrafish sequence, similar cell-cycle genes, tumor suppressors, and oncogenes are present. Large scale, forward genetic screens can target these highly conserved cancer pathways. The transparent, rapidly developing embryos are amenable to mutagenesis screens that examine cell-cycle phenotypes like cell proliferation, cell differentiation and genomic instability. Genetically engineered zebrafish have clarified the biological similarity between stem cells and cancer, especially the signaling pathway called "Notch," first named for fruit flies that had disruptions in the pathway resulting in notched wings. In zebrafish and humans, pathways like Notch send chemical messages to cells starting an intracellular cascade of changes to the cells' function or identity.





Early in zebrafish and human development, Notch actively directs embryonic cells to differentiate into specific tissues. Then, the Notch pathway rests. Cancer cells can activate the Notch pathway in adults, causing cellular chaos like T-ALL. Clinical trials are underway to see if shutting down Notch can help. Other researchers are building on the connections between the Notch pathway and stem cell formation to see if stimulating Notch will increase the number of blood stem cells in bone marrow, enriching the marrow before it is transplanted and perhaps giving patients an alternative to today's bone marrow transplants.

This tiny fish, native to the Ganges River in India, may replace the lab

mouse as an experimental animal/tool in certain genetic studies. The Zebrafish requires less space, is cheaper than the laboratory mouse, and spawns about 2,000 progeny annually compared to the mouse's meager 48 offspring per year. It has already lead to a better understanding of human diseases of the heart, aorta, and brain. Studies are underway in certain cancers, muscular dystrophy, and ocular and auditory disorders.

*Fish get cancer, bait does not.

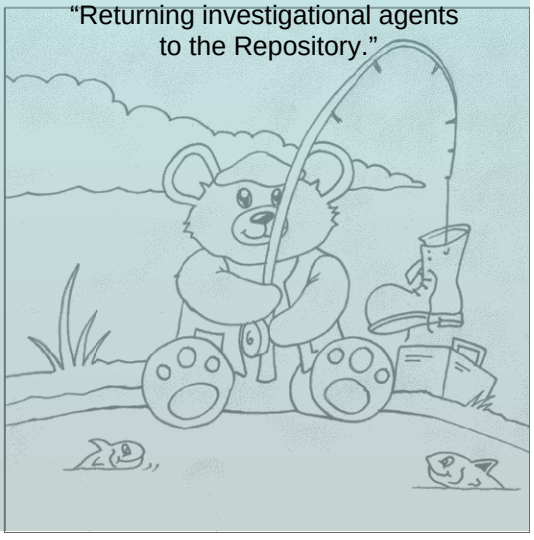
References available upon request.

Not Quite What We Were Fishing For...

It's so annoying when you've patiently waited for a trout to nibble all day, and when it finally does...it's a moldy boot! When we open a box of returns only to find partial bottles of agent that should have been destroyed according to a site's local destruction policy--and the returns are wrapped in disposable diapers!--we feel the same way. (We wish we were making this up!)

- Only return items that you received from us to us. We have a whale of a time with other stuff.
- Return only intact, unopened bottles, vials, units, boxes.....
- Be sure to fill out the Return Drug List accurately and completely. Find the current version (which is a pdf writable form) at **http://ctep.cancer.gov/forms/Return_June_2006.pdf**.
- Note that the NCI Division of Cancer Prevention has their own version of the Form 986. It is not interchangeable with the CTEP version of the Form 986. Please make sure you use the form that includes the 627 Lofstand Lane return address!
- Please don't write in the areas of the Return Drug List designated for NCI Use Only.
- Carefully pack materials to keep them from breaking during transit; if all you have is clean disposable diapers, so be it. Don't let breakables flounder around in the box.
- Please write "RETURNS" prominently on the outside of the container to help the repository separate returns from new shipments of agents to the repository.

Need more help? E-mail pmbafterhours@mail.nih.gov and ask for the PMB FAQ, "Returning investigational agents to the Repository."



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CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING (CINV)

GREEN AROUND THE GILLS MOTION SICKNESS/ SEA SICKNESS

Pathophysiology

Chemotherapy induces nausea and vomiting by activating one or more of the following mechanisms:
- Direct or indirect stimulation of the chemoreceptor trigger zone (CTZ); the CTZ, located in the floor of the fourth ventricle outside of the blood-brain barrier, is responsible for most CINV
- Peripheral stimulation of the vagus nerve in the gastrointestinal (GI) tract
- Vestibular mechanisms
- Cortical mechanisms, or
- Taste and smell alterations

The central nervous system (CNS) coordinates all motion stimuli. Sensory information from head and body's position or movement is sent via cranial nerve VIII. Sense of equilibrium is maintained by a complex interaction of the
- Inner ear (labyrinth): coordinates direction of motion stimulus in turning, forward-backward, side-to-side, and up-and-down.
- Eyes: indicate body position in space, and direction of motion.
- Skin pressure receptors (joint and spine): indicate the body touching the ground.
- Muscle and joint sensory receptors: indicate movement of the body.

MOA

Exact MOA is unknown. It is postulated that the vomiting center is triggered by various neurotransmitters released by CTZ activation. Some major neurotransmitters responsible for CINV include dopamine, serotonin, histamine, norepinephrine, and substance P. The role of other enzymes like MAO, cholinesterase, and catecholamine located around the CTZ is poorly understood in CINV.

Movement deviations in the inner ear, eyes, skin or muscle receptors create conflicting messages that are received by the CNS as disequilibrium or imbalance, resulting in the motion sickness.

Signs and Symptoms

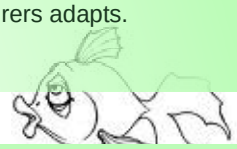
Nausea, vomiting, dehydration, imbalanced electrolytes, weight loss, and slow healing wounds.

Nausea, vomiting, pallor, and cold sweat

Onset and duration

- Acute: within few minutes to several hours following therapy and lasting up to six hours.
- Delayed: usually > 24 hours post chemotherapy lasting up to seven days
- Anticipatory: a conditioned response affecting people with prior experiences with the severe CINV. It can occur before, during, or after chemotherapy administration.

- Depends on individual susceptibility to the magnitude of the motion stimulus.
- Order of incidence: Boat voyage > aircraft > car > train
- Usually resolves following termination of the motion stimulus, or disappears as the sufferers adapts.



Risk Factors

Patients undergoing chemotherapy treatment; People with histories of motion sickness or morning sickness during pregnancy; younger age; Non-drinkers

Children: 2 – 12 years of age; female gender [women > men (1.7: 1)]; menstruation; pregnancy; people with migraine headaches

Treatment

Prevention is based on the emesis risk of the chemotherapy administered. Acute and delayed emesis is classified into four categories: high, moderate, low, and minimal.

For example:
- Acute high risk CINV is usually treated with a 5-HT_3–receptor antagonist (5HT_3RA) + corticosteroid on day 1.
- Delayed high risk might be treated with dexamethasone + a 5-HT_3 RA and a dopamine antagonist on days 2 to 4.
- Anticipatory: benzodiazepine plus antiemetic agents before and during chemotherapy; techniques in relaxation, desensitization, and hypnosis can be effective.

Additional treatment information can be found in the NCCN Guidelines-Emesis, or DeVita, 7th edition,.

Self–control:
- Choose front seat of a car; middle seat of the plane or boat.
- Minimize head and body movements
- Avoid reading; focus on the horizon or on a stable object.
- Meditation before the preciptating event.

Medications: Base choice on the trip's duration, underlying medical condition, and the amount of sedation.
- Patch (scopolamine): Long trip; apply four hours prior to departure; change every 3 days.
- Oral (scopolamine, diphenhydramine, dimenhydrinate, promethazine, meclizine): short trip: take one hour prior to departure; effective for several hours. Dimenhydrinate and diphenhydramine are appropriate for use in children.