



# INSIDE PMB

## AUGUST 2007

### Four Years? Fabulous!

According to Cher (who is having or has had her numerous tattoos removed), "For someone who likes tattoos, the most precious thing is bare skin." Here at PMB, the most precious thing is getting the word out to you in a way that just might tempt you to read it. Inside PMB enters its fifth year of publication with this issue, and even we are amazed that (1) we've lasted this long, (2) you still read and respond to us, and (3) that the censors have yet to tell us to clean up our act. In these four years--or for at least the last three of them--we have tried to use a metaphor or theme to make the message fun. This issue's theme, tattoo, gives us another opportunity to ink paper.

#### Riddle: How are tattoos and investigational drugs similar?

Summer is the worst season in which to be tattooed. Tans and tattoos don't mix; sun ruins tats' bright, bold colors (black fades, too). Over time, repeated sun exposure fades tattoos like it fades construction paper left in a window.

Summer is the worst time to ship investigational agents, as the temperature rises to almost unbearable numbers. We ship all agents according to manufacturer-provided guidelines, and we supplement it with a little common sense. When temperatures are extremely hot (Hello Phoenix!), we ship refrigerated agents late in our day for arrival early in the stifling destination's day. Some refrigerated agents that are normally shipped Priority mail are sent by FedEx next day delivery as well.

Call us if you have questions about agent shipment.



**LOOK FOR INSIDE PMB QUARTERLY  
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#### Artists vs. Scratchers

In the tattoo world, there are two types of tattooists: artists and scratchers. "Artist" is self-explanatory. A scratcher is a person who attempts to tattoo with no knowledge of technique or sterilization procedures.

In the drug ordering world, we have artists and scratchers, too. Real artists will download the most recent version of the NIH Form 986, Clinical Drug Request from the CTEP web site ( go to [ctep.cancer.gov](http://ctep.cancer.gov), and then select FORMS in the yellow bar). The current version has a line for your E-mail address, which will help us help you.

A random sample of 52 orders sent as this newsletter was going to press revealed that only 25% of our customers fell into the artist category. The remainder were using old, and sometimes very old, CDRs. Scratchers, please update your form.

#### Is It Permanent Ink?

Q: Does the NCI accept electronic signatures on electronic drug accountability records?

A: If the system electronically captures the initials based on signing in with user names and passwords and the initials can't be edited by another user, NCI accepts the electronic initial. If the initial field is of the "free text" variety where anyone could add anything then the document must be printed and signed by the appropriate pharmacist(s).

### Decisions You'll Regret in the Future

*I see a woman with a tattoo, and I'm thinking, okay, here's a gal who's capable of making a decision she'll regret in the future. ~Richard Jeni*

Slang	Tattoo Meaning	PMB Analogy
<b>Vow</b>	A design incorporating a name ("Mom," "Betty Sue," "Chuckie 4-ever")	Using an agent's trivial name (e.g. PS-341 ) in clinical records long after the agent is commercially approved. Once a generic is assigned, please start using it.
<b>Cover-up</b>	A new, hopefully better, tattoo placed over an existing and unwanted one (see "Vow" above)	Using white-out over an error. White-out is not allowed on official records; please line through, initial, and make a clear correction.
<b>B-Back</b>	A customer who says, "I gotta run to the ATM, I'll be back" and never returns.	A person who PMB calls for information on an order, who says they will call back in 10 minutes, but doesn't. The order sits unfilled.
<b>Fall Out</b>	Rapid fading color in a new tattoo due to improper application	What happens years after you have returned an agent to the NCI without completing all the blanks on the paperwork. The NCI has no record of what you did, and you have nothing to show an auditor.
<b>Zero Hour</b>	The time of your appointment for your first tattoo	When you ask permission to transfer an agent after the fact, only to find out we must officially deny it. The denial becomes part of the permanent record, as it's too late to cancel the actual transfer.
<b>Cadaver</b>	Customers who refuse to talk to the artist during the entire tattooing process	Agents that sit on your shelves for more than 90 days after you received a PMB-generated stock recovery letter.

## Yojjukugo

心願成就

Shin Gan Jo Ju  
Heart Wish Thing Achieve

You've probably seen folks tattooed with a string of four Japanese characters, often on their necks or arms. *Yojjukugo* are Japanese compound words made of four kanji characters. The yojjukugo's specific meaning cannot be inferred from the meanings of the individual kanji, because the kanji are like synergistic agents--their meaning together is greater and more profound than when taken alone. The yojjukugo above, shinganjo-ju, means "If you wish a thing in your heart, it will be achieved."

Which brings us to PMB's Blinded Studies team, and the four wishes in their hearts.

心

Their hearts desire that you have the NCI-assigned protocol number on your lips when you call about patient-specific drug.

願

Their wish: that you have the patient ID number that has been assigned by the lead group ready, too.

成

The thing they need next is the patient's initials to confirm they are checking on the correct patient.

就

To achieve your objective, they'll want to confirm the registering investigators name and NCI number.

起承轉結

Ki-sho-ken-tetsu

Start, Continue, Change, Conclusion

## Sweet 16s

The oral c-MET inhibitor AZD6244 will be available as powder in boxes containing 16 bottles for oral suspension. Its blow filled seals (BFS) of Captisol diluent that is added right before you administer the agent will also be available in 16s. PMB will not break boxes. One box = 16 bottles, so order by the box, OK? Find mixing instructions in the protocol and on each box.

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Brought to you by the Coalition of Homeless Squirrels



## DMB Completes Divotal Trial; Endpoints Met

PMB recently completed a pilot project on "ink transfer." Its objective: Determine if we could harvest fewer trees while receiving faxed Clinical Drug Request (CDR;NIH - 986) forms. The method: Converting the main drug order fax line from the old paper-based fax system to a new paperless Electronic Fax (EFax) transmission system. Using it, PMB receives, views, processes, and files all faxed CDR's electronically.

What potential adverse events were described in the informed consent?

1. The EFax process is transparent to senders.
2. You will experience NO physical or psychological changes in the way you fax CDR forms to PMB.
3. You will continue to fax drug order requests to the same fax number located on the CDR form: (301) 480-4612.

The findings: Faxes sent by EFax system have higher survival rates (measured in fax transmissions that actually make it to us) than those navigating the paper fax system. EFax provides a more efficient workflow, allowing CDR forms and any resulting questions to be processed even faster than before.

The real world application: This transparent transition is scheduled for activation some time in August 2007.

PMB thanks consenting sites and subjects for participating in the EFax Pilot Program:

Brad Christensen and Jackie Heim from Mayo Clinic Rochester, MN

Scott Fields at the University of California San Francisco Medical Center, CA

Emmanuel Semmes, Mark Miller, and Phyllis Newson at the University of Chicago, IL

## Tattooing the Gluteus to the MAXIMUS

When you decide to be tattooed, you can pick a tattoo from a selection of standard tattoos, or you can design your own--the artists call this "custom work." We had an interesting question on pmbafterhours recently that highlights the same is somewhat true of some of our forms.

Apparently, the folks at SHANDS at the University of Florida got an NIH Drug Accountability Record Form (DARF; NIH Form 2564) from Johns Hopkins in Baltimore. On the gluteus (or rear) of Hopkins's form, there was a lovely table for additional comments. SHANDS asked PMB why said comment form did not appear on the back of the electronic version of the DARF posted on the CTEP web site.

The simple answer: A master artist at Johns Hopkins tacked the "additional comments" form onto the back of our form.

The NCI has created only the front of the DARF and it is posted on our web site. The DARF is generic and rarely meets all needs at the institution level. While you must not alter DARF's front page, some sites are making very good use of the form's blank back to capture additional information important to their individual site. This is acceptable.

So, don't change the front, but feel free to use the gluteus to the maximus to meet your institution's specific needs.

PMB's forms are easily downloaded from  
<http://ctep.cancer.gov/forms/index.html>

## Don't Forget Your Moko

During the 1800s in New Zealand, native Maoris's intricate facial tattoos, or "moko," were not only body art, but also the individual's legal identity. Whenever a tribal chief needed to sign his name to a European document, he painstakingly drew his entire facial design.



That said, PMB has no compunction about reminding you that all orders for investigational agents must be signed by an authorized designee, since most of you will not have a moko to copy.

### And also...

▶ The shipping address you provide on the clinical drug request must match the address that is listed in NCI's Database from the Investigator's 1572.

▶ Sites may order up to an eight week supply for most protocols. PMB does not allow you to place drug orders within 10 days of your last shipment.

## Avoid Geeking: Tattoo Tips

**(1) Never tattoo something that is likely to change, like a paramour's name, in a visible place.** Example: If you'd tattooed

"AZD2171" on your bicep, you'd have to have it replaced with its NSC (732208) which never changes; cediranib (the new generic); or Recen-tin® (its new trade name). OUCH! Note that this agent's tablet look and bottle sizes are changing, too. Look for this change soon.



**(2) Once a tattoo heals, use sunblock; some parlors will provide a template so you can apply sunblock only to the tattoo, and tan the rest of your gorgeous self.** And speaking of light, it's no longer necessary to mix CCI-779 in a darkened hood. Just protect it from sunlight and excessive room light. The final product's stability is now six hours. Note that commercial Torisel® is mixed differently than the investigational product.

**(3) If your employer forbids visible tattoos, consider an ultraviolet tattoo that is nearly invisible in normal light, but a brilliant blue under black light.** Less-than-invisible will be this change at PMB: We will be sending commercial dasatinib (NSC 732517; Sprycel®) 50 mg tablets in bottles of 60 for an interim period due to a shortage of investigationally labeled bottles of 30 tablets.

## Sorry, Can't Help You There!

☒ From pmbafterhours@mail.nih.gov: "Please send me the expiration dates of the following physicians." Please note that PMB has no idea when individual physicians become cadavers. We can only tell you when their investigator registration numbers will expire. Use pmbafterhours if you have five or more numbers to check, please.

## Contest Winner!

Mary Dover, BSMT, CCRP, of Jonesboro, Arkansas for updated her 1986 Return Drug List; Margie Peterson of Duluth, MN for updating her 12/94 Clinical Drug Request; and Tom Kostecki, RPH of Madison, WI (his oldest form was dated 12/95).

## Almost Indelible: Informative Ink

- Need an Investigator Brochure for an agent for which NCI holds the IND? E-mail to [ibcoordinator@mail.nih.gov](mailto:ibcoordinator@mail.nih.gov) or call 301-496-5725 and ask for the IB Coordinator.
- Have investigator registration questions? E-mail [PMBregpend@mail.nci.nih.gov](mailto:PMBregpend@mail.nci.nih.gov) or call 301-496-5725 and ask for the Registration Coordinator.
- Want to request agent for non-human use? Send an E-mail to [PMBafterhours@mail.nih.gov](mailto:PMBafterhours@mail.nih.gov) and use the subject, "ATTN: NHU Coordinator." Or call the NHU Coordinator here at PMB.
- Have issues with investigator-held INDs? Send an E-mail to [PMBafterhours@mail.nih.gov](mailto:PMBafterhours@mail.nih.gov) and use the subject, "ATTN: Investigator-Held IND Coordinator."
- Questions about a foreign shipment? We have a coordinator for those, too! Send E-mail to [PMBafterhours@mail.nih.gov](mailto:PMBafterhours@mail.nih.gov) and use the subject, "ATTN: Foreign Shipment Coordinator."

## NEEDLES AND THE FAQ:

**Question: Can we use a filter needle or an in-line filter with agent X?**

Answer: Sites sometimes call and ask if they can use a filter needle, even though the protocol does not call for one. Sometimes it's because they see particulate matter, and sometimes it's because they use a standard infusion set that has a built-in filter. Official guidelines are hard to find, and often, companies are slow to respond to PMB's queries.

Basically, filters come in three sizes:

- ▶ A 0.2 or 0.22 micron filter is a sterility filter. It can filter out bacterial contaminants. Studies have found that the contamination rate of pharmacy-prepared sterile products approaches 5%, so in some cases, using an in-line filter is a good idea. It will also catch particulate matter, but the filter may clog and slow the infusion.
- ▶ A 1.2 micron filter is a safety filter, and will catch particulate matter while allowing the drug solution to continue unimpeded.
- ▶ A 5 micron filter is also a safety filter, but clearly more porous.

One might think that the size of the agent molecule would determine whether it can be filtered or not. For example, those ginormous monoclonal antibodies might clog a 0.2 micron filter, right? Not necessarily. It is more an issue of the molecule's electrostatic affinity for the filter. Almost all agents are passed through a 0.22 micron filter during the packaging process to ensure sterility, and most agents pass through this size filter with no problem. Sometimes, however, the agent adheres to the filter, and if that is the case, the mass of the agent administered is the determinant in whether to use a filter or not. A general guideline is that when a dose is given in micro or nanograms, and its affinity for the filter is unknown, do not use a filter because if it does adhere, 10% or more of the dose might be lost. If a dose is given in mg amounts, even if it does adhere, the mass in the filter is small compared to the total dose, and little drug is lost.

What are the consequences of inadvertently administering particles to patients? If a solution containing particles is administered intravenously, it bypasses normal defense mechanisms. Particles larger than 5 microns are apt to lodge in the pulmonary system. Normal, healthy individuals usually have no repercussions. The concern is greater, however, with

- ▶ large volume, long term IVs, like total parenteral nutrition
- ▶ in premature infants whose lungs are undeveloped
- ▶ in patients who are compromised.



## Ten Facts: Radiosensitizers

Talk about tattoos in oncology circles, and clinicians will chatter about radiation, since radiologists tattoo their patient with small temporary marks or permanent India ink tattoos that precisely pinpoint the area needing treatment. Tattoos are more precise and durable than Magic Marker lines. But radiation alone is rarely a good strategy. There's been great interest, but little success, in radiosensitizers. This quick fact list will keep you abreast:



- ▶ Radiosensitizer: an agent that sensitizes tumor cells to radiation therapy. The ideal (but currently nonexistent) radiosensitizer would reach the tumor in adequate concentrations, spare healthy tissue, possess predictable pharmacokinetics for timing with radiation, and lack toxicity.
- ▶ Chemotherapy and radiation can be synergistic by inducing DNA base damage or single or double strand breaks, or targeting different cell cycle phases. The G2-M phase is the most radiosensitive whereas the S phase is the most radioresistant. Chemotherapy can inhibit post radiation damage repair.
- ▶ Chemoradiotherapy is currently used in several cancers: head and neck, lung, esophageal, rectal, gastric, pancreatic, cervical, bladder, glioblastoma, and sarcoma.
- ▶ Commercial agents with radiosensitizing properties include cisplatin, 5-fluorouracil, capecitabine, gemcitabine, hydroxyurea, mitomycin-C, temozolomide, and paclitaxel.
- ▶ Hypoxia is common in many cancers, and a maker of poor clinical prognosis. Reactive oxygen species (ROS), which require oxygen, are thought to be essential for the cytotoxic effects of radiation. Hypoxic cells are 2.5 to 3 times more radioresistant than normoxic cells.

### PMB distributes two investigational agents with radiosensitizing potential: tirapazamine and motexafin gadolinium.

▶ Tirapazamine has about a 100 fold increase in potency in anoxic conditions. In hypoxic conditions, tirapazamine releases a free radical electron causing DNA damage. In normoxic tissues, these radicals quickly bind to oxygen re-establishing the parent compound.



- ▶ Cell repair after radiation requires an active pool of reducing, electron-donor substrates (i.e. intracellular reducing metabolites or "antioxidants" like glutathione, ascorbic acid, flavins, and NADPH). Motexafin gadolinium (MgD) is an avid electron acceptor that preferentially oxidizes electrons from these reducing substrates. This depletes the pool of intracellular oxidants, enhancing radiation damage.
- ▶ Receiving MgD is like getting a tattoo from the inside out! It's a brilliant green, and patients' skin often turns a lovely hue
- ▶ MgD is well tolerated and shows promise in

NSCLC brain metastasis. Due to the presence of gadolinium, pharmacokinetic imaging can be performed by MRI. [Except when the patient has a new tattoo! Fresh tattoos may be incompatible with MRIs because they contain metal salts. Even folks with older tattoos may feel pain or heat when they undergo MRI.]

▶ Downstream signaling pathway overexpression can mediate repopulation of tenacious tumor cells after radiation. EGFR inhibitors, antiangiogenics and other targeted therapies may block signaling pathways responsible for aggressive tumors and radioresistance.

### Contest: Make PMB Laugh

Here's the deal: It's not easy thinking up newsletter motifs. We've done Rome, fashion, Mother Nature, Broadway, the jungle... We've asked you to update your forms. It's time for all those creative people hiding in hoods and clinics, hospitals and healthcare facilities, to step up to the plate.

E-mail us at [pmbafterhours@mail.nih.gov](mailto:pmbafterhours@mail.nih.gov). Suggest a motif for the next newsletter, and explain why it is a good idea in 50 words or less. The winner's essay will be published (if possible), and authors of the three best essays will get cookies or homemade dog biscuits.

## Tattoo Deterrent?

Approximately 25% of Americans are tattoo canvas, and 30% to 50% of women aged 45 to 70 years have permanent makeup on or around the eyes, lips, and eyebrows. Some chronologically challenged (read as: older) and more conservative people try to discourage their kids from plumping up these statistics. Could concerned individuals wave the red flag of cancer as a deterrent?

We know some facts. The Food and Drug Administration does not regulate tattoo pigments or their ingredients, which is in itself one concern. Additionally, tattooing has been associated with a variety of complications, including inflammatory reactions, infection transmission (leprosy, tuberculosis cutis, syphilis, hepatitis, herpes simplex, herpes zoster, and warts), and neoplasms. No conclusive data links tattoos and cancers, but there are case reports-melanoma, basil cell carcinoma and squamous cell carcinoma-in patients who have had tattoos. Folks with body suits (heavily tattooed) may have trouble seeing cutaneous cancers, which could delay treatment.

Red pigments are the most common cause of delayed tattoo reaction. Mercury in red mercuric sulfide is usually the cause. In most cases, allergic reactions are caused by para phenylenediamine (PPD). PPD can trigger dermatitis with serious consequences. We'd love to tell you which dyes pose greatest risk, but since not all dyes contain PPD and the FDA doesn't regulate tattoo dyes...you get the picture. PPD is added to henna-based temporary tattoos to enhance precision and darken designs, so beware.



And, PPD is the main aromatic amine used in hair dye. Some epidemiologic studies have suggested that use of PPD-based hair dyes might increase risk of human malignant tumors including bladder cancer and he-

matopoietic cancers. One study done showed that women who dyed their hair before 1980 were at a higher risk for cancer than those who employed hair dye after 1980. However, researchers have not consistently observed associations between personal hair dye use and cancer.

So. It's unclear whether tattoo ink causes cancer. A stronger argument against tattoos may be that removing with laser may force aforementioned unidentified toxins and carcinogens to lodge in the lymph nodes. Twenty-five per cent of people with tattoos would like to have them removed. And the inks--particularly yellow and orange--are very difficult to remove completely. But recently, a tattoo removal expert invented a new dye that is biodegradable, and more safely removed.