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National Cancer Institute
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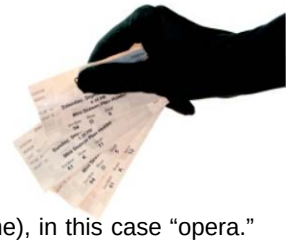
This issue's theme:

A Night at the Opera



Every issue of INSIDE PMB is like an opera. We decide on a leitmotif (theme), in this case "opera." Then we decide what to spotlight, and the tone. The research begins, and we learn about the theme, and apply it to our recent news. A soloist might write a feature, while duets work on broader issues. Then, our newsletter diva attacks the design.

In this issue

- we encourage you to practice, practice, practice using OAOP (see below)
- we think that our patient page (page 4) will steal the show; and
- we provide a little oratorio about pesky drug supply problems (page 2)

One of our pharmacists (who went to see Man of La Mancha, which may or may not be an opera, in the 8th grade), suggested a color scheme of burgundy, black and gold. Sadly, we could not make gold using available tools. We googled this problem, and were advised that converting gold to flat color delivers a color like baby poo. So use you imagination, and when you see a muddy yellow, think gold flecks.

So...silence all phones, beepers and pagers and enjoy!

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Ixabepilone dilution: Singing a new tune!

Data on drug dilutions matures like the voice of a classically trained contralto. Some of you may remember ixabepilone when it was costumed as an investigational drug called BMS-247550. The only infusion fluid we could support was lactated ringer's injection; that presented a hardship for some sites (you may already know this if you use commercial agent or conduct studies under the company's IND). More recently the company has allowed normal saline. If you wish to use normal saline, you must adjust the diluent pH by adding 2 mEq sodium bicarbonate (2 mL of an 8.4% w/v solution or 4 mL of a 4.2% w/v solution) to each 250-mL bag of normal saline. The prepared product is stable for 6 hours when the final concentration is between 0.2 mg/mL to 0.6 mg/mL. Hallelujah!

Anticipate Unanticipated Closures; Become an Ordering Virtuoso

It's January, and all of the United States (except maybe Hawaii) have had some inclement weather issues. The first 27 days of January 2011 have been snow-filled in the unlikeliest places! You may recall that just a year ago, PMB closed for an entire week when this area was incapacitated by Snowmageddon 2010. Some of us are singing an almost prayerful "O Sole Mio" (My Sun), while there's a small recitative (half singing, tuneful talking) chorus of "Come on snow! Come on snow!" But we are ready. Are you?

At this time, all sites can order in two ways. You can fax your orders, or you can use our new Online Agent Order Processing (OAOP) application. This application replicates and improves the current manual process. Find it at

https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx

Very shortly, on-line ordering will replace the fill-out-the-form-and-fax-it-and-hope-it-goes-through process. OAOP is full of e-mail notifications and self check-out options!

If PMB must close for any reason–and although the tenors are singing for sun and the chorus wants snow, the complete score hasn't been written yet–you're better off using OAOP to order. No kidding. So sign up for OAOP today. You'll give yourself a standing ovation when you're done!

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Cancer Institute

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Could it be Resonant Frequency?

Recently, we've dealt with several problems related to glass particles in vials, problems so serious that we have had to recover stock or severely limit distribution. Some manufacturers have indicated the glass flakes result from interaction of the active agent with the glass vials over the product's shelf life. Others have said that delamination (layer separation after repeated cyclic stress or impact) is the cause.

We know that singing can shatter glass if the soloist's resonant frequency matches the glass's resonant frequency. So let us put forth this theory: Maybe people who work in pharmacies or clinical trials voice their overheated feelings with singing full of trills and runs, and the resonant frequency in their upper registers is causing the glass to flake. Maybe. Maybe not.

Regardless, we appreciate your cooperation when we experience serious supply problems. Which leads us to…

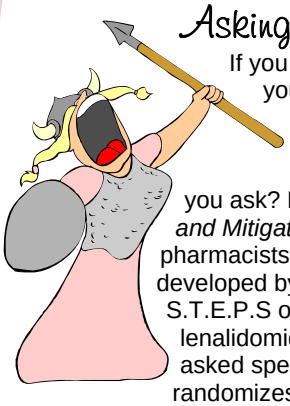
Your Comedy, Our Drama

When PMB pharmacists must handle serious supply situations, one of their first steps is to look at all recent and incoming clinical drug requests for the agent. The purpose: They estimate how many patients are currently being treated. During a recent near-crisis, here is what we found: Some sites make stuff up! They "guesstimate" the number of patients being treated. Can you believe it?

Please make a concerted effort to ensure that the information you provide on your CDR (or better—through OAOP—see page 1) is correct.

And please note that supply problems are not over until the fat lady sings, and she can sometimes be in the wings warming up for a very long time!

Lenalidomide and Thalidomide: Asking for a translation



If you have an NCI-sponsored protocol at your site that includes thalidomide and/or lenalidomide and these agents are provided by PMB, you needn't use REMS! What is REMS, you ask? REMS stands for *Risk Evaluation and Mitigation Strategies*. Dispensing pharmacists would normally follow REMS developed by Celgene and the FDA , either S.T.E.P.S or RevAssist, for thalidomide or lenalidomide respectively. A few of you have asked specifically about E1A06, a trial that randomizes patients to one of two arms containing either thalidomide or lenalidomide. Since these agents are provided to sites under CTEP's IND, the FDA has given us permission to proceed without REMS. There is one stipulation. We (and subsequently, you) must follow the same guidance that REMS uses. For example:

- You can only dispense a 28-day supply
- You must counsel with every cycle
- All females of childbearing potential must have a pregnancy test with every cycle

Each protocol spells out dispensing details. If this tune sounds like Die Zauberflöte to you, then call PMB or email us at PMBafterhours@mail.nih.gov and we will be happy to translate. Please don't call Celgene to register NCI study participants unless your protocol tells you to!

What if the patient is on a protocol's maintenance phase and doesn't need to come to clinic every month? Patients who remain on study treatment using either thalidomide or lenalidomide need to return to clinic every 28 days for additional drug, counseling, etc. (see protocol for dispensing guidelines). No exceptions. And please don't mail refills! Mailing CTEP-supplied investigational agent is not allowed, and considered a protocol deviation. We call this "operatic jam session" when you adlib instead of following the score. If you have already "deviated from the protocol," please notify PMB and your local IRB, and make a notation on the DARF.

Brava, Bravo, Bravi!

A recent stock recovery for bevacizumab 100 mg or placebo vials (all lots) generated a flurry of calls to PMB. The letter contained no lot numbers since all 100 mg size vials were to expire at the end of 2010. And, these vials had been used exclusively on CTEP sponsored BLINDED studies since September 2007, when the open label supply changed to 400 mg vials.

So here is a shout-out: when you receive stock recovery letters, read carefully and ask yourself these questions:

1. Is there a lot number?
   a. BRAVO! = open label
   b. BOO! = blinded
2. Is there a patient number on each vial?
   a. BRAVA! = blinded
   b. BOO! = open label
3. What is the strength being recovered? This is always listed on the letter.
4. Does the stock recovery include placebo vials? That's a clue to a blinded study.
5. Will one letter come for both blinded and open label supplies? Absolutamente no, PMB sends separate letters for blinded supplies and open label supplies.
6. How can I tell if it is for blinded or open label?
   a. PMB recovers blinded supplies using a Julian date. The letter will ask you to return any supplies received prior to "X" Julian date.
   b. PMB recovers open label supplies using lot numbers regardless of when you received the supplies.

STANDING ROOM ONLY

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P-glycoprotein: Guarding the Stage Door, Bouncing Intruders

Question: Several of our protocols refer to P-glycoprotein (P-gp) substrates or inhibitors. Is there a list of these agents available, and what is the specific concern about P-gp?
Answer: Drugs are processed predominately via two mechanisms. One is via the liver's CYP enzyme system. The other is via plasma membrane proteins, especially P-glycoprotein, a drug transport mechanism that has the ability to actively pump drugs out of cell membranes and cytoplasm (see Box 1). Since our goal is to get the agent into the cell, P-gp works against us in most cases.

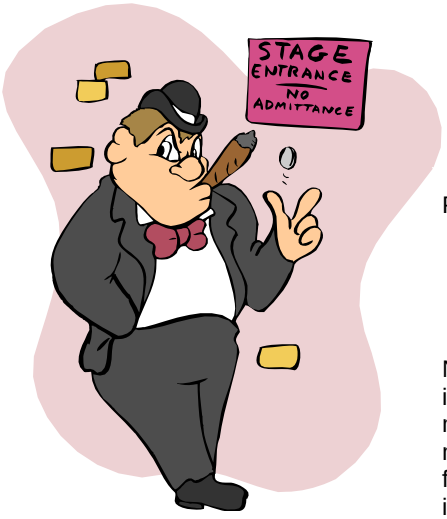
These proteins are hard-wired into our genetic code as multidrug resistance (MDR) genes, and are quite hardy. Humans have two MDR genes, MRD1 and MDR3 (also called MDR2), but only MDR1 is implicated in drug transport. A number of tumor cells exhibit multidrug resistance to chemotherapeutic drugs because they overexpress P-glycoprotein. P-gp is also an integral part of the blood-brain barrier. MDR1 encoded P-gp has also been implicated in the cytotoxicity process and plays a role in oxidative and inflammatory processes. P-gp may also

- be involved in steroid and lipid transport and metabolism
- modulate expression of CYP3A, thus complicating drug-drug interaction predictions
- be controlled by a variety of endogenous and environmental stimuli that evoke stress responses including cytotoxic agents, heat shock, radiation, genotoxic stress, inflammation, inflammatory mediators, cytokines and growth factors.

Box 1. Using ATP as an energy source, P-gp can transport certain hydrophobic substances in the following directions:
- •into the gut
- •out of the brain
- •into urine
- •into bile
- •out of the gonads
- •out of other organs

Molecules interacting with P-gp may be classified as substrates, inhibitors or inducers. Substrates, in being transported, do not block the transport of other substrates; the substrates that move through the P-gp pump can be transported simultaneously with other substrates. Inhibitors may promote substrates' transport into the cell, thereby potentially restoring cell sensitivity and overcoming multidrug resistance. Inducers activate P-gp and are believed to reduce pharmacologic activity of the substrate.

P-gp substrates have diverse structures, but are usually hydrophobic amphipathic molecules (molecules having two sides with characteristically different properties) that are not negatively charged, and may be 200-1800 Da in size. They include
- Antineoplastics: doxorubicin, daunorubicin, vinblastine, vincristine, actinomycin D, paclitaxel, teniposide and etoposide;
- Immunosuppressants: cyclosporin A, tacrolimus and sirolimus;
- Steroids: aldosterone, hydrocortisone, cortisol, corticosterone, methylprednisolone and dexamethasone;
- HIV protease inhibitors: amprenavir (APV), indinavir (IDV), nelfinavir (NFV), ritonavir (RTV) and saquinavir (SQV);
- Miscellaneous agents: terfenadine, morphine, digoxin, quinidine, lovastatin, atorvastatin, domperidone, ondansetron, loperamide, colchicines, erythromycin, rifampicin, ivermectin; and the fluorescent dye rhodamine-123.Under certain circumstances, P-gp may be able to transport hydrophilic negatively charged compounds, such as methotrexate.



P-gp inhibitors include
- cyclosporin A and its non-immunosuppressive analogue PSC833 (valspodar), sirolimus and tacrolimus;
- verapamil;
- HIV protease inhibitors: RTV, SQV, NFV and possibly IDV;
- Miscellaneous agents: mifepristone (RU486), quinidine, midazolam, tamoxifen, erythromycin, ketoconazole

P-gp inducers include
- cyclosporin A, sirolimus and tacrolimus;
- cisplatin, daunorubicin, doxorubicin, fluorouracil, etoposide and methotrexate
- dexamethasone, erythromycin, morphine and tamoxifen

Note that some drugs appear on more than one list, and we've included agents that are investigational or that have been taken off the market just to be complete. Their functions may change depending on their concentration or the patient's diagnosis, concurrent medications, or stressors. Additional study is underway to elucidate P-gp's role and also to find ways to modulate P-gp that take advantage of potentially beneficial drug-drug interactions.

~References available upon request~

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Patient Page

Patient pill diaries can be a drama or a comedy if patients aren't trained to use them appropriately. How often do patients return with diaries that make no sense or seem to have been completed in the parking lot? Too often! Taking a few minutes to review the pill diary and explain how to complete it can make a huge difference. Following up with written information helps, too. Although many pill diaries have directions for patients written on them, the information is often truncated and squeezed into a small space so the diary will fit on one page. This patient information page is designed for you to give it to patients after counseling.

Keeping a Medication or Pill Diary? Read This First!

It's important to take your medication according to your treatment plan for the best results possible. Because you are on a clinical trial, your treatment team needs to be sure you take all your medicine correctly. They also need to know if you have side effects or problems. They will give you a "pill diary" (also called a "medicine diary") to help you to keep tract of your daily medicine. The pill diary will also remind you

- how many times a day you should take your medication
- how often you must take it
- how many tablets or capsules (pills) you should take for each dose (and sometimes, you'll use this diary for injectable medicine that you give yourself)
- that you need to talk to the doctor, nurse or pharmacist about concerns.

Now, how do you use your this diary?

1. Each line of your "pill diary" is numbered sequentially.
2. As you fill in this diary, do not skip any lines. Each line is for one entry. Use the line to record that you took your medicine and any side effects if you have them.
3. Record each dose as soon as you take it. Do not wait until later! If you wait, you may forget important information.
4. Fill in the date. For example, if you take a dose on January 13, 2011, write down "1/13/2011."
5. Write each dose on a separate line. That is, if you are taking one dose in the morning at 9 AM and one in the evening at 9 PM, you should make two entries—one for 9 AM and one for 9 PM.
6. Make a mistake? To correct a mistake, make a single line through that entry and write "error." Don't scribble over your entry, or blot it out with ink. Just draw a single line through it. Go to the next line and re-enter the date, number of pills, and any comments.
7. If you forget to take a dose, read the directions about missed doses or call your healthcare team and ask what to do.
8. If you cannot make up the missed dose, write the date and "dose missed" or "dose skipped" in the "Comments" column and explain why.
9. If you experienced side effects such as nausea, headache, describe them in the "Comments" column. Write the date that the side effects occurred.

If you record each dose and side effect in your pill diary, your healthcare team can assess your progress better. They may also be able to decide if you really had a side effect or if the symptom may have been caused by something else. Bring your pill diary with you to every appointment. And remember—record your doses as soon as you take them. Don't wait until you are in the parking lot getting ready to go to your next appointment!

Where should I keep my pill diary?

Keep your pill diary with your medicine in a cool, dry place. Here's a tip: you can roll your diary and attach it to your medication bottle with a rubber band, or place the pill diary and your medicine together in a zip lock bag.

Find PMB's Frequently Asked Questions at http://ctep.cancer.gov/branches/pmb/faq.htm.

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