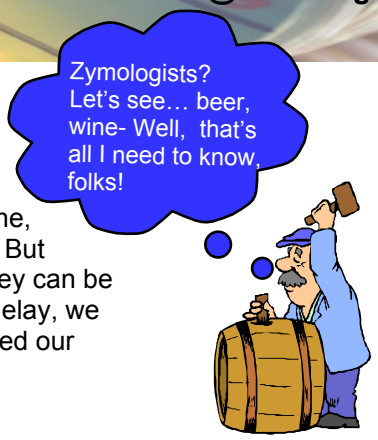
INSIDE PMB

November 2012

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
Email: PMBAfterHours@mail.nih.gov

THIS ISSUE'S THEME: Fermentation



This issue is for all you budding *zymologists* out there! The wha…? Ok, our issue is targeted to all those interested in the science of fermentation, which includes everyone, because really, who's not interested in bread, cheese or wine, the most ancient foods? But microbes do so much more, like spew out useful antibiotics and antineoplastics, and they can be manipulated to mass produce molecularly engineered compounds. So without further delay, we dedicate our issue to all the unicellular pharmaceutical manufacturers that have inhabited our planet since the beginning of time.

Better Living Through Microbes

We benefit every day from fermentation. Besides what we eat and drink, fermented products also supply us with treatments for disease. Fermentation-based technology using microorganisms, usually cultured in aerobic conditions, has played a historic role in pharmaceutical development and continues to find new roles for cancer treatment.

Here are some examples of older commercial agents and CTEP distributed agents listed with their respective bacteria that made their production possible. (see table)

Manufacturing of recombinant products, such as granulocyte colony-stimulating factors, interferons, antibodies, and vaccines, also utilizes fermentation technology. One investigational agent you might see in a future CTEP-sponsored trial is a recombinant yeast-based (*Saccharomyces cerevisiae*) vector vaccine, GI-6207 (NSC 745968). A plasmid vector containing the modified human CEA gene is used to transfect the parental yeast strain (*S. cerevisiae* W303 - a haploid strain with known mutations from wild-type yeast) to produce the final recombinant vaccine product. Vials of GI-6207 for injection actually list yeast units as the unit of measure!

Commercially available agents	CTEP distributed agents
Products of fermentation by *Streptomyces* species: Actinomycin D (NSC 3053) - *S. parvullus* Mitomycin C (NSC 26980) - *S. caespitosus* Daunorubicin (NSC 82151) - *S. peucetius* Doxorubicin (NSC 123127) - *S. peucetius* Bleomycin (NSC 125066) - *S. verticillus*	Product of fermentation by *Myxobacterium Sorangium cellulosum:* Ixabepilone (NSC 710428) (also commercially available) Product of fermentation by *Chromobacterium violaceum:* Romidepsin (NSC 630176) (also commercially available)

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

OAOP Reminders:

Courier Number

The courier number is not a required field in the OAOP ordering screen. Please do not provide a courier number unless you want us to use it.

On the other hand, if you enter a 'need by date' that is sooner than 5 business days from the ordering date for ground shipment orders, you must provide a courier number in order to expedite receipt of the shipment.

OAOP Emails

When you receive a system-generated email from OAOP, please do not reply to it. If you reply directly to the email, your reply will end up in the trub (sediment at the bottom of a beer fermenter) never to be seen again. Instead, use the link that's embedded within the email message.

Food Poisoning vs Beneficial Spoilage

Problem: You overhear one of your patients in the clinic talking about gorging at next weekend's Oktoberfest. You know this patient just started a cycle of BEACOPP on a cooperative group study for Hodgkin's lymphoma.
Hint: BEACOPP contains procarbazine.

Solution: As you start salivating and thinking that your lunch seems really lame right now, get your mind back to the bratwurst, sauerkraut and brew. What do they all have in common? Fermentation and tyramine, of course!

Did you know that tyramine is produced during fermentation? It's one of those chemicals produced during beneficial spoilage or what we refer to as pickling, aging, marinating or fermenting. It is also a source for food poisoning for patients who are taking a monoamine oxidase (MAO) inhibitor like procarbazine (NSC 77213). Tyramine requires MAO for metabolism and because procarbazine inhibits MAO, the resulting interaction with tyramine-containing foods can produce a hypertensive crisis. Some patients may only experience a migraine headache, but it's best to inform patients that certain foods can make them sick. Patients receiving a MAO inhibitor like procarbazine should also avoid any concurrent use of medications with MAO inhibitory activity like linezolid.

The more aged/rotten the food, the higher tyramine content! Fermented food and beverages high in tyramine include:

Dairy based: cheese (blue, brie, camembert, cheddar, gruyere, mozzarella, parmesan, romano)

Meat/Fish based: sausage, air dried or fermented (eg, pepperoni, salami, summer sausage, bologna [high levels of tyramine]), meat, poultry, or fish (potentially spoiled), shrimp paste

Fruit/Vegetable based: bean curd, fermented tofu, canned figs, sauerkraut (very high levels of tyramine), soy sauce, soybean paste, soya and fava beans, sherry, wine (in general), chianti

Adapted from *Drug Interaction Facts™: Herbal Supplements and Food.* © Wolters Kluwer Health, April 2009

Coming Soon!!
Drug Accountability Report Form (DARF) for Oral Agents

PMB is happy to announce the development of a new DARF specifically for oral agents. The form has been submitted to the Office of Management and Budget (OMB) as part of the triennial renewal process under the Paperwork Reduction Act. We expect this form will be approved early 2013 and implemented in Spring 2013. The existing document will still be referred to as the DARF and will continue to be used for injectable agents while the new form will be designated DARF (Oral) and will be used for oral agents. The DARF (Oral) is oriented horizontally (landscape) and has columns to account for patient returns. A sneak peak is available below.

More information will be available as we approach first quarter 2013.

Print Form | Save As | Reset Form

Collection of this information is authorized under 21 CFR 312.57. This information is collected to ensure compliance with Food and Drug Administration (FDA) requirements for NCI as an NDI sponsor and that investigational agents are under the control and accounted for by competent authority. The information may be disclosed to researchers for investigational purposes, sponsors of clinical trials and their company collaborators, the applicable Institutional Review Board, NCI, FDA and Department of Health and Human Services. Submission of this information is voluntary, however, in order for you to conduct a study in accordance with relevant, current protocols, you must complete all fields.

Form Approved: OMB No. 0925-0613 Expires: xx/xx/20xx

Public reporting burden for this collection of information is estimated to average 4 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to: NIH, Project Clearance Branch, 6705 Rockledge Drive, MSC 7974, Bethesda, MD 20892-7974, ATTN: PRA (0925-0613). Do not return the completed form to this address.

Investigational Agent Accountability Record
Oral agents ONLY

National Institutes of Health
National Cancer Institute
Division of Cancer Treatment and Diagnosis
Cancer Therapy Evaluation Program

PAGE NO.
CONTROL RECORD ☐
SATELLITE RECORD ☐

Name of Institution:	Investigator Name:		NCI Investigator No
Protocol Title:	NCI Protocol No:	Local Protocol No:	Dispensing Area
Agent Name:	Dose Form and Strength.		Bottle size (e.g., # tablets/bottle):

Line No.	Date	Patient's Initials	Patient's ID No.	Dose	Quantity Dispensed or Received	Balance Forward / Balance	Manufacturer and Lot No.	Recorder's Initials	Expiration Date (if available)	Date Patient Returned	Quantity Patient Returned	Recorder's Initials
1.												
2.												
3.												
4.												
5.												

No Immunity at PMB Against Drug Shortages

Requests for local destruction and agent transfers suggest that sites have excessive inventory. Remember that the NCI is not immune to shortage of investigational agents. Drug sitting on your shelf is drug that is not available to another site that may need it. It's also a lot of time and money that could be spent elsewhere.

We know how it happens: a new study is approved at your site so you order a supply of the investigational agent in every available dosage form. Two years later, the study has not accrued any patients and the supply has expired.

Or, after receiving the requested 8 week supply, you learn the subject has been off study for 3 weeks!

Or, you're notified of the upcoming expiration of an agent. In order to stay on top of things, you order enough to replace the current supply.

Whatever the reason, the end result is under-utilized drug on the shelf. PMB suggests the following to avoid this situation:

- Wait to order until a patient is being evaluated for the trial. Check the protocol for the maximum number of days allowed between patient registration and the first dose of therapy.
- Work with research staff to notify you when a patient is being screened for or coming off treatment.
- Dispense from the expiring supply **IF** the patient(s) will complete the cycle / supply prior to the expiration date.
- Place orders closer to the anticipated dispense date.
- Make sure someone on your team receives notices from PMB regarding expiration dates, study closures, etc. Timely action may allow you to transfer agents from one trial to another before the expiration date. Notices are sent to the site PI and shipping designee, so please make sure they are being forwarded appropriately.

Keep Reading...

PMB's staff sends out a stock recovery letter for an agent and you did not receive it. "Why was I not on the distribution list?" you ask. PMB emails letters 30 to 60 days prior to the agent's "Best By" date or as soon as the drug company confirms that the agent is likely to spoil past a certain date. Our letters go to two parties only:

- The shipping designee who is listed on the agent order at the time of the order
- The investigator's current address per the FDA 1572

Postscript: We know you have things TNTC (too numerous to count) going on in the pharmacy. You should effervesce with delight to know that access to stock recovery letters will be included in a new OAOP module update. Date: TBD (to be determined).

Folks! You do not need to use overnight express courier services to expedite the return of agent to the NCI Clinical Repository. Controlled temperature packaging is NOT necessary. Pack the agent in ziplock bags with adequate protection to prevent breakage. Use GROUND SHIPMENT. You will save **$!**

CHEERS FOR A JOB WELL DONE

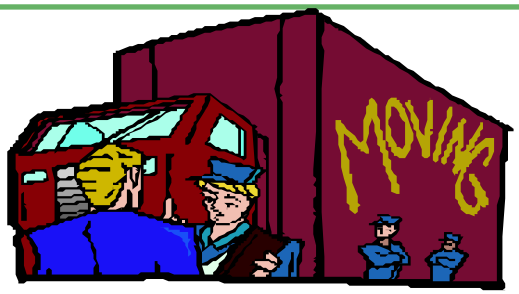
It had to happen eventually.

It is with mixed feelings the PMB staff said good bye to a valued and trusted friend and staff member, Pat Schettino. On August 31, 2012, Pat retired after 20 years in the Pharmaceutical Management Branch at CTEP and even more time at the NIH Clinical Center and the joint NCI/Navy Oncology Pharmacy at the National Naval Medical Center, Bethesda. I say mixed feelings because although her presence and advice will be sorely missed, we acknowledge that we are truly happy that she could transition into that much sought after province of retirement we all look forward to.

There was no question that Pat could not answer. Her knowledge of the policies and procedures that drive CTEP and especially PMB was limitless. She knew the policy, when and why it was implemented, but also whose idea it was and how the policy interacted with other policies and procedures. She knew the organization from top to bottom. She was the go to person for almost everything.

All of CTEP wishes her well in retirement, where she can take on the responsibility of just being the Grandma. Pat, we thank you for all of your contributions and your steadfast dedication and wish you a very happy and fruitful retirement.

Skip Hall, PMB Branch Chief

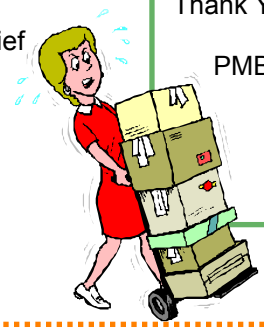


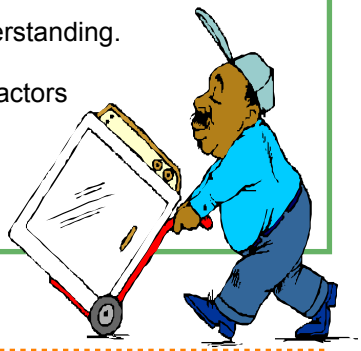
HEADS UP

The Pharmaceutical Management Branch (PMB), along with many other NCI offices, will move in March 2013 to a new location. This major relocation will move almost all PMB resources to a new building located about 5 miles from our current offices. We hope to retain the main PMB telephone number, but we have no assurances of this at this time. We do not expect a final determination until after January 1, 2013. If the request is granted little will change for our customers, but if a change is required, it will be a major disruption for those of you who call us. We anticipate no disruption of e-mail or delivery service from the NCI Repository. We will keep you apprised as we get closer to our move-in date.

Thank You for your understanding.

PMB Staff and Contractors





Faxed Orders Still Percolating in the System

While 99.9% of you comply with electronic agent orders submission using OAOP, there are a few repeat offenders who continue to fax agent orders.

PMB does not accept faxed orders.

Please refer to the FAQ that outlines necessary steps for using OAOP.
http://ctep.cancer.gov/branches/pmb/faq/docs/how_to_access_oaop.pdf

If you need help, call us at 301-496-5725 or email
PMBafterhours@mail.nih.gov