INSIDE PMB

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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: OLYMPICS

Originally inspired by the Greek gods on Mount Olympus, humankind has celebrated physical perfection and performance through the Olympic Games. Although PMB neither existed at the start of the ancient or modern Games nor has any noteworthy athletic abilities, we do pray to the heavens above for clinical trials perfection in the electronic age and have racked up our own record-breaking statistics for 2012. We'll showcase some of them for you plus provide coverage of various PMB events.

New Olympic Event: Oral Investigational Agent Repackaging

Just like the Olympic athletes who strive to attain excellence in both technical difficulty and execution, we apply the same to repackaging of oral investigational agents. Often information on the stability of investigational agents is limited or unknown therefore making repackaging an important consideration when dispensing oral investigational agents. Currently, PMB has stability information to support the following:

Agents that may be repackaged
Vorinostat (NSC 701852)
Sorafenib (NSC 724772)
Lenalidomide (NSC 703813)

Agents that may NOT be repackaged
MK-1775 (NSC 751084)
Dasatinib (NSC 732517)
MLN8237 (NSC 747888)
PCI-32765 (NSC 748645)
XL184 (NSC 761968)*

** XL184 tablets are stable for up to 24 hours when dispensed in an open container, such as in a pill cup, and are stable for up to 7 days when dispensed in a closed container, such as a pharmacy dispensing bottle.*

Keep in mind that for most PMB agents, it's unknown if and to what extent repackaging could impact the stability and therefore we cannot recommend repackaging. This is where the technical factors and customized execution enter the judging. Technical factors such as quantity per cycle, total bottle quantity and patient visit frequency should be considered and dispensing should be executed according to the protocol. For example, the protocol may say to:

- Dispense an exact quantity for one cycle, which may require repackaging
- Dispense an exact quantity for one cycle in the manufactures bottle, which may require wasting
- Dispense the intact bottle, allowing for extra doses which can be counted as a patient return

NOTE: Please do not repackage blinded agents without PMB authorization

Always refer to the protocol for the latest information since it can change faster than Usain Bolt running the 100 meter sprint!

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

Projectile Capsules

A dabrafenib capsule took off like a shot-put from the bottle and rolled onto the pharmacy floor. You aren't sure what to do with it now that it's contaminated. Hint: It's no longer suitable for clinical use.

In the case of the shot-put capsule, you need to record this on the DARF so that 100% of the inventory is accounted for. So arrange for onsite destruction for your contaminated capsule. PMB has an FAQ that helps you troubleshoot drug inventory discrepancies. http://ctep.cancer.gov/branches/pmb/faq/docs/darf_discrepancies.pdf

If a patient loses a capsule at home, then it doesn't affect the DARF unless the patient really needs one more capsule dispensed before the next visit. Then this dispense should be accounted for on the DARF with the appropriate notation.

Anti-doping vs. Clinical Trial Audits

Large institutions must have rules and policies to ensure that everyone is playing by the same rules. During the London Olympics, the International Olympic Committee collected 5000 samples from athletes for anti-doping analysis, more than at any previous Olympic games. Like the IOC, DCTD manages large numbers--it sponsored 158 new trials in 2012. The responsibility of the Clinical Trials Monitoring Branch (CTMB) is to find the outliers according to rules and regulations set forth by the FDA. Read the scenario below and identify the irregularities:

PMB ships agents to the pharmacy of a hospital. The receiving staff calls clinic staff from the building across the street to pick up the agents to store and dispense to patients. The shipping receipt and the control DARFs are maintained by the clinic, not the pharmacy. The audit team found the receiving pharmacy was not retaining the shipping receipts or maintaining the control DARF. At the re-audit, the team discovered the clinic was using a satellite DARF; there was no control DARF. Also, the investigator had not implemented the corrective action plan from the earlier audit because other auditing groups had since rated the hospital pharmacy and clinic as "acceptable." What are the issues?

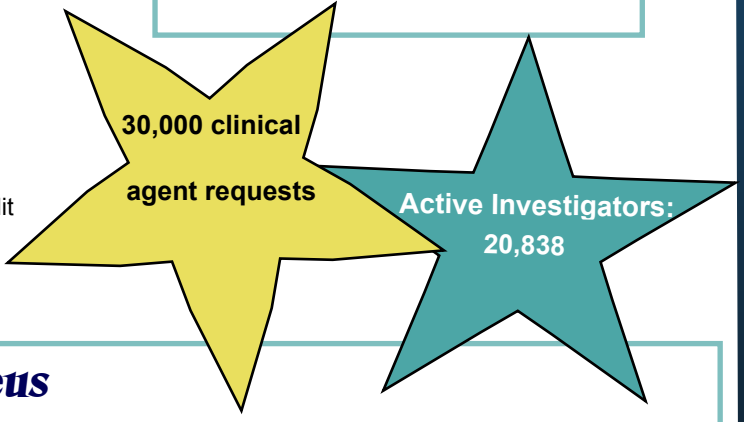
1. A control DARF needs to be maintained along with the shipping records at the pharmacy.
2. Satellite DARFs are required in the clinic.
3. The investigator neither implemented the corrective action plan nor notified the auditing group as to why it wasn't implemented.

Generally, audit outcomes may produce different results since auditing group practices vary. Regardless of the outcome from another group's audit, the investigator must respond to each audit independently and implement the appropriate corrective action plan.

(Imagine being a world-class cyclist and answering to each anti-doping agency individually; IOC, USADA and WADA.) If a site does not implement a corrective action plan based on the results of another group's audit, the investigator must notify the original auditing group (who notifies CTMB) and provide a rationale. The group and CTMB will determine if this is acceptable. Refer to http://ctep.cancer.gov/branches/ctmb/clinicalTrials/monitoring_coop_ccop_ctsu.htm for more information about corrective action plans and auditing guidelines.

PMB Policy

PMB policy requires that shipping receipts and control DARFs be maintained where agents are received, in this case, the pharmacy. A satellite DARF is required any time agents are transported to another area for storage and dispensing (the clinic). One hundred percent of the agent inventory must be accounted for on the control DARF even if it is not present in the control area. Refer to http://ctep.cancer.gov/branches/pmb/agent_management.htm for more information.



PMB Operations During Acts of Zeus

PMB staff is dedicated to providing responsive and reliable service. We developed a plan many years ago to ensure that shipments of investigational agents to institutions continue during inclement weather or other emergencies, but even Hercules could not contend with today's challenges in infrastructure and technology such as:

- Operating status of regional airports and shipping companies (FedEx, UPS, etc.)
- Connectivity with NCI computer systems/servers and staff working remotely

As weather and other circumstances become more unpredictable, we recommend that sites stay prepared for these events. Things you can do now include:

- Keeping IAM accounts and passwords current
- Updating shipping and ordering designees on the supplemental investigator data forms
- Anticipating inclement weather in the Washington DC region that would impact your ability to receive shipments from PMB
- Disseminating PMB correspondence appropriately within your institution

During these times, it is best to communicate with us using the PMBafterhours@mail.nih.gov e-mail address. PMB staff members will respond as quickly as possible depending on connectivity status. Deliveries will restart when the shippers and airports are operating.

Exercise Isn't Just for Olympians

Even mere mortals can reap the many benefits of regular exercise, including preventing cancer. But recent studies show that exercise significantly improves disease-free survival (DFS) and overall survival (OS) in healthy patients after cancer diagnosis. At least nine MET-hours per week of activity can improve DFS by 10% and OS by almost 30% according to a CALGB analysis of stage III colon cancer patients one MET (metabolic equivalent task) equals the energy spent sitting for one hour.[1] An analysis of the Nurses' Health Study cohort of women with non-metastatic breast cancer showed a similar result with obese women deriving the most benefit (0.22 relative risk of death from breast cancer with 15-23.9 MET-hours per week compared to <3 MET-hours per week).[2] Likewise a large Chinese study demonstrated an OS benefit of 35% within the first 18 months for women with non-metastatic breast cancer who expended at least 8.3 MET-hours per week.[3]

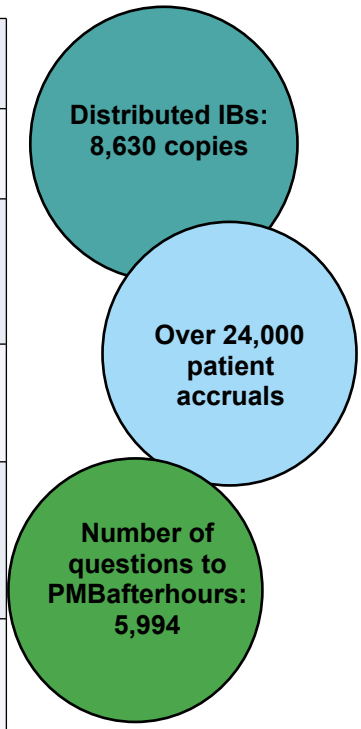
The lesson here is that your patients don't have to look like Michael Phelps before they get into the pool. For example, a leisurely breaststroke for a 60 kg person over 30 minutes is 10 MET value or 300 kcal. MET values and energy calculations can be found in the Compendium of Physical Activities.[4]

1. Meyerhardt JA et al. Impact of physical activity on cancer recurrence and survival in patients with stage III colon cancer: findings from CALGB 89803. J Clin Oncol 2006;24:3535-41.
2. Holmes MD et al. Physical activity and survival after breast cancer diagnosis. JAMA 2005;293:2479-86.
3. Chen X et al. Exercise after diagnosis of breast cancer in association with survival. Cancer Prev Res 2011;4:1409-18.
4. Ainsworth BE et al. Compendium of physical activities: classification of energy costs of human physical activities. Med Sci Sports Exerc 1993;25:71-80.

Para-Olympics for PMB Agents

Sometimes our agents need to be managed outside of the mainstream process. Here are a few special events that you may want to schedule on your DVR for later viewing.

Agent/Strength	NSC	Affected Protocol/s	Action
Nelarabine (506U78)	686673	AALL0434	Recall letter sent October 11, 2012 for lot C533169
Lenalidomide (CC-5013)	703813	CALGB-100104	PMB is no longer supplying lenalidomide after December 15, 2012 (refer to protocol update #16)
AZD2171 (cediranib) 2.5 mg and 10 mg tablets	732208	Various AZD2171 protocols	Stock recovery letters sent; strengths no longer available for clinical trials research
Bevacizumab or placebo	704865	CALGB-90601, GOG-0250, RTOG-0825	Stock recovery letter sent for all supplies received prior to Julian Date 12331 (last shipped on November 26, 2012)
Bortezomib (PS-341, Velcade)	681239	All	Vial cap is now gray (formerly blue) – no other changes to product
VEGF-Trap (aflibercept)	724770	All	Generic name changed to ziv-aflibercept; current supply suitable for clinical use until 3/31/13 expiration



Bulletin Board

Note: PMB moving date is March 2013. Our new address as of March 25th:

If sending by United States Postal Service (USPS):
National Institutes of Health/
National Cancer Institute
Pharmaceutical Management Branch, CTEP, DCTD
9609 MEDICAL CENTER DR
RM 5W228 MSC 9725
BETHESDA, MD 20892-9725

If sending by Express Courier (FedEx, UPS, etc.)
National Institutes of Health/
National Cancer Institute
Pharmaceutical Management Branch, CTEP, DCTD
9609 MEDICAL CENTER DR
RM 5W228 MSC 9725
ROCKVILLE, MD 20850

New phone number will be available soon.

PMB web page: 11,000 visits per month

158 studies were activated

New Players

Every few years we get a new team of agents for NCI-sponsored clinical research. You may have seen some of them in action already, but as spectators watching for the next big star, check these out:

Player (Agent Name)	Team (NSC#)	Team position (Target)	Field (Admin. Route)
ABT-263 (navitoclax)	750238	Small molecule inhibitor of Bcl-2 family of proteins	Oral
AMG 386	751173	Peptibody that targets angiopoietin 1 and 2	IV
ARQ 197 (tivantinib)	750832	Small molecule inhibitor of the c-Met	Oral
Dabrafenib mesylate	763760	Small molecule inhibitor of BRAF	Oral
GSK2141795	767034	Small molecule inhibitor of Akt	Oral
MLN8237 (alisertib)	747888	Small molecule inhibitor of Aurora A	Oral
MK-1775	751084	Small molecule inhibitor of Wee-1	Oral
OSI-906	751082	Small molecule dual kinase inhibitor of IGF-1R and IR	Oral
PCI-32765 (ibrutinib)	748645	Small molecule inhibitor of BTK	Oral
Pomalidomide	767909	Immunomodulatory agent	Oral
SCH727965 (dinaciclib)	747135	Small molecule of cyclin-dependent kinase	IV
Trametinib DMSO	763093	Small molecule inhibitor of MEK1/2	Oral
TL32711 (Birinapant)	756502	Small molecule Smac mimetic and IAP inhibitor	IV
TRC 105	754227	Monoclonal antibody for CD105	IV
XL184 (cabozantinib s-malate)	761968	Small molecule inhibitor of C-Met and VEGFR2	Oral

PMB Hurdling Revisited

Every three years, PMB enters into the 110 day sprint with the Office of Management and Budget (OMB) for renewal of the DARF and investigator registration (IR) forms. You may notice that on February 28, 2013, the IR forms will expire. If we don't make it to the finish line in time, continue to use the existing forms even if expired. For questions, contact the PMB Registration Help Desk at PMBRegPend@ctep.nci.nih.gov