Clean, Green, Mean!

INSIDE THIS ISSUE:

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INSIDE PMB

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Four Facts: Stability Testing

Stability testing of Drug Product (the FDA's term for the final formulated dosage form in its immediate packaging) is a mean business. It's purpose? To establish shelf-life and storage requirements for subsequent lots of the product manufactured, packaged and stored under similar conditions. Stability testing of the Drug Substance (e.g., FDA lingo again for bulk substance or unformulated drug used to produce the final dosage form) is also an important part of the overall stability evaluation.

1) Drug Products with an expected shelf-life of more than 12 months are typically tested every three months for the first year, every six months for the second year and annually thereafter to assess identity, purity and potency of the product.
2) Accelerated stability testing is a means to an end—by using storage conditions outside of the proposed storage condition, the tester looks for increases (or decreases) in the drug's rate of chemical or physical changes. In other words, it assesses the effects of short-term temperature excursions.
3) The stability protocol may also evaluate the container closure system. A container closure system is designed to protect the dosage form from factors that can alter stability and sterility—light, moisture and microbial contamination. But container closure systems have been known to cause loss of potency, leaching of chemicals, precipitation, etc. For this reason, during stability testing, vials of an injectable solution may be stored upside down to assess the drug product's interaction with the stopper and potential changes in composition.
4) Types of testing vary greatly among drugs and biologics, dosage formulations and regulatory requirements across countries. It is not a "one-size-fits-all" process and involves more in-depth requirements than briefly described here.

Hate to Burst your Bubble...BUT...

We sometimes receive Clinical Drug Requests (CDRs; NIH Form 986) that are of unacceptable quality. Many customers seem annoyed when we call and ask them to resend a clean copy.

- Now many of you think we are the end of the line and report to no one, but we (like you) must sometimes produce documentation of our work. And it has to be legible and complete.
- Please keep your forms clean and tidy. CDRs are not the place for smudgy scribbles or traces of your lunch!
- If you've made it to a job in an investigational drug pharmacy or program, you probably have a good idea if your hand-writing is bad. Got a bad case of chicken scratch? Our forms are available on the web site as "pdf writeables." Go to http://ctep.cancer.gov/forms/, and look for Requisition of Agents. You can type right into the form!
- If you don't have time to do it right the first time, you surely won't have time to do it over! And that time-saving practice of pre-filling a form and using it over and over (and over and over) is costing you time if we have to call back. Here's a shocker for you: a pre-filled form has a half life of about five copies, and the print fades like a cheap temporary tattoo in a soapy bathtub. It also shifts a millimeter to the margin every time you copy. Pretty soon, "The Best Little Cancer Center in the US" is "est Little Cancer Center in the US, and then "ittle Cancer Center in the US"
- Forget, "Just use the address in your database." Can't do it, and that's all we're going to say about that.
- Let's put a plug in here for using the most current version of the form, again available at http://ctep.cancer.gov/forms/. The most current CDR is dated 02/2007 in the lower left-hand corner.

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Green Approach to Medicine Disposal: Keeps Kids Safe and Water Clean!

Medicines are critical for diagnosis, treatment, alteration, or prevention of disease, but they must be disposed of properly to prevent harm. Community organizations, healthcare leaders, federal, state, and accreditation organizations are all in a lather about drug disposal. Why? It's a matter of not only human health and safety, but also environment pollution.

Generally, unwanted, unused, leftover pharmaceuticals and personal care products enter into the environment via sewage or landfill runoff. We need to be better about providing patients with appropriate disposal instructions. What should we say at a minimum?

- Do not flush prescription drugs down the toilet or drain, except as described below.
- Use hospital, clinic, community drug take-back programs or programs for household hazardous waste collection if your city or county government's household trash and recycling service allows it.
- If all else fails, dispose of prescription and OTC drugs in the house hold trash after removing the patient's name (but not the drug name). Tell patients to adulterate it with an undesirable substance, such as cat litter or used coffee grounds. Then, seal it in an opaque bag and throw it into the household trash right before it is picked up.

Medicines approved by the FDA to be disposed by flushing can be found in the table listed below; it's important for oncology staff to be familiar with this list, because all of these are controlled substances, most used for pain . The FDA is confident that the benefits of using the "flush disposal" method for this select list of medicines outweigh the risk of polluting our water supply. Why? Flushing eliminates the possibility of life-threatening risks from accidental ingestion of these drugs.

So, the disposal guidelines for general prescription drugs are pretty clear, but vary depending on what resources the patient has available. The guidelines for disposal of chemotherapy or "hazardous" drugs—and all-inclusive term for cytotoxic, hormones, antibiotics, etc—is somewhat ambiguous in the home setting. And, patients who have expired or excess IND agents must return these agents to the clinic for proper disposal, and they must be accounted for by the clinical trial's management—that's very straightforward!

It's OK to Flush These Medications!

Medicine	***Active Ingredient***
Actiq, oral transmucosal lozenge *****	Fentanyl Citrate
Avinza, capsules (extended release)	Morphine Sulfate
Daytrana, transdermal patch system	Methylphenidate
Demerol, tablets *****	Meperidine Hydrochloride
Demerol, oral solution *****	Meperidine Hydrochloride
Diastat/Diastat AcuDial, rectal gel	Diazepam
Dilaudid, tablets *****	Hydromorphone Hydrochloride
Dilaudid, oral liquid *****	Hydromorphone Hydrochloride
Dolophine Hydrochloride, tablets *****	Methadone Hydrochloride
Duragesic, patch (extended release) *****	Fentanyl
Embeda, capsules (extended release)	Morphine Sulfate; Naltrexone Hydrochloride
Exalgo, tablets (extended release)	Hydromorphone Hydrochloride
Fentora, tablets (buccal)	Fentanyl Citrate
Kadian, capsules (extended release)	Morphine Sulfate
Methadone Hydrochloride, oral solution *****	Methadone Hydrochloride
Methadose, tablets *****	Methadone Hydrochloride
Morphine Sulfate, tablets (immediate release) *****	Morphine Sulfate
Morphine Sulfate, oral solution *****	Morphine Sulfate
MS Contin, tablets (extended release) *****	Morphine Sulfate
Onsolis, soluble film (buccal)	Fentanyl Citrate
Opana, tablets (immediate release)	Oxymorphone Hydrochloride
Opana ER, tablets (extended release)	Oxymorphone Hydrochloride
Oramorph SR, tablets (sustained release)	Morphine Sulfate
Oxycontin, tablets (extended release) *	Oxycodone Hydrochloride
Percocet, tablets *****	Acetaminophen; Oxycodone Hydrochloride
Percodan, tablets *****	Aspirin; Oxycodone Hydrochloride
Xyrem, oral solution	Sodium Oxybate

*Medications marked with an asterisk have generic versions available, or are only available as generic drugs.

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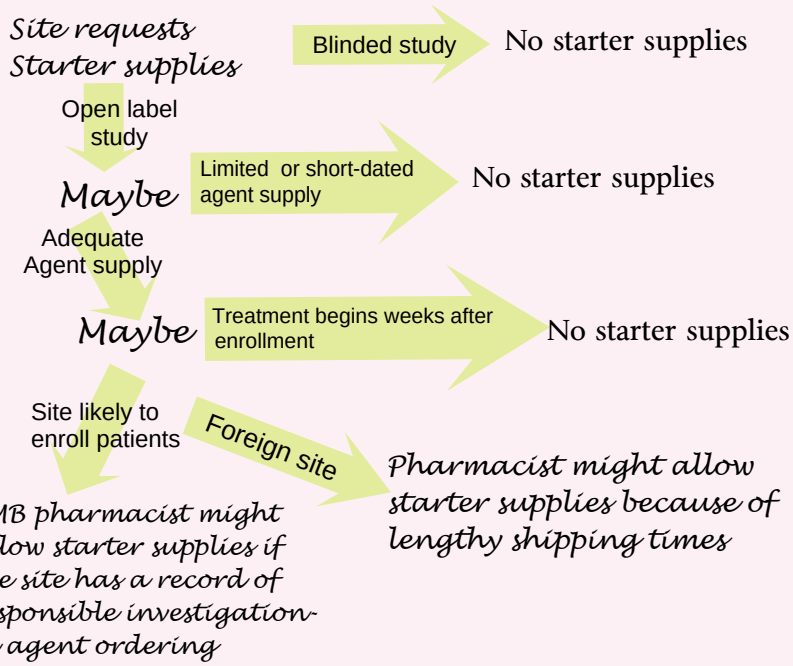
Green From the Get-Go
A Narrative of Starter Supplies

A loyal but frustrated PMB employee asked us to explain all there is to know about "starter supplies." (Loyal readers may recognize this information as recycled from a previous issue!) Starter supplies, if you are unfamiliar with the term, are supplies sent when the protocol is open at your site, but no patients have enrolled yet. The PMB pharmacist responsible for the agent you ~~wish to stock-pile~~ want in anticipation of enrollment makes the decision about starter supplies. It goes a little like this:



So the decision to send or not to send starter supplies is based on numerous factors invisible to sites. Pharmacists at PMB are concerned about a number of issues, including the environment. Ordering starter supplies for patients who will probably never materialize is like taking 50 napkins when you pick up your carry-out lunch because you may spill! (You do that? Well stop it, it's wasteful.)

Please think carefully before ordering starter supplies. In addition, these steps are good clinical practice and environmentally friendly!

- Dispense smaller, rather than larger, quantities of PRN medications. Fewer doses will expire or be wasted if the patient doesn't need them.
- Encourage prescribers to use the lowest effective dose.
- Discontinue unnecessary drugs.

Let this be our mantra: A drug avoided is a drug that is not excreted into our water supply!

PMBafterhours

Do you have a question and need an answer soon,
but not necessarily right this minute?
E-mail pmbafterhours@mail.nih.gov
Any time day or night!
Expect an answer on the next business day.

FAQ: My actual drug inventory doesn't match the quantities reflected on the Drug Accountability Record Form. What should I do?

We really climb onto our soapbox on this issue. Investigate this problem much like you would investigate a controlled substance ledger error:

(1) Check your math. Often, people add or subtract incorrectly, leading to discrepancies. Remember that when you correct errors, you should line through with a single line, and initial all changes. Do not use correction fluid, or obscure the entry with blobs of ink.

(2) Missing investigational agent?
•Check all potential storage areas. Is it possible some of the missing agent was slipped into a bag belonging to a drug with a sound-alike or look-alike name?
•Check charts of patients who are on the study. Did staff forget to record the dose given to a patient recently?

(3) Too much investigational agent?
•Did staff log out investigational agent for a patient who failed to appear or was turned away because of low blood counts? Did they return it to stock but forget to change the balance?
•Did they log out the right investigational agent, and then use commercial drug accidentally?
•Is another agent short the same amount? Did they log out the right investigational agent, and then use the wrong investigational agent?

(4) Stamp your feet and yell, "Yes!" if you're half a bubble off plumb with relief or "OH DIRTY DOG!" if you've done all this and it's no soap.

Once you've conducted your investigation, you've either found the agent, or written an incident report to wipe the slate clean. In the latter case, make an entry on the Drug Accountability Record Form (DARF; NIH 2564) indicating that you are correcting the balance, and referring to your internal incident report. Keep a copy of the incident report attached to the DARF in question.

They Work Hard So You Don't Have to...

The Institute of Medicine released its report on NCI Cooperative Groups on April 15, 2010. They analyze what works, and what doesn't work, and make recommendations for improvement.

Find the report at http://tinyurl.com/y24ck4k (look in the upper right hand corner to get the report on line for free).

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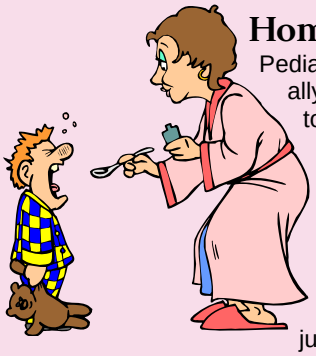

Home Ad Hoc P&A: A Fuzzy Process Until Now

Pediatric trials often begin after investigators find the recommended adult phase 2 doses, and clinical trials usually begin before companies develop a pediatric formulation. Often, cancer patients and their families have to manipulate CTEP IND drugs at home, especially when the study subject is an infant or child who cannot swallow capsules or tablets. This is called *ad hoc preparation*; it is reformulation of available adult dosage forms, i.e., capsules, tablets, or intravenous preparations. It can be a messy procedure. Ad-hoc preparation and administration (P&A) is a necessary, but temporary measure until the agent's manufacturer makes a more pharmaceutically elegant pediatric dose.

To support ad-hoc P&A, our collaborating drug companies provide short term stability data. Usually, patients or their caregivers open capsules and sprinkle the content onto food (e.g., applesauce or apple juice) and take the preparation within 30 minutes (this varies depending on the agent). Long term stability data (e.g. supporting at least 7 days of storage) support extemporaneous compounding by trained pharmacists in a dedicated compounding area accessible to authorized personnel only.

Ad hoc P&A has some identified issues. Lack of dose uniformity—for example, adherence of the agent to the vessel wall if no suspending agent is used—can cause inaccurate dosing, and patients will not get the full dose. When that happens, all that work goes down the drain! The ad-hoc formulation's pK may differ from that of intact capsules or tablets. We had a brush with this kind of problem. The phase I erlotinib pharmacokinetic study (*J Clin Oncol 26:4921-4927, 2008*) demonstrated that patients who took erlotinib oral suspension had higher AUCs than those who took tablets. Additionally, we surveyed sites to see what safe handling information they gave patients and caregivers. There was tremendous variation. Using a standardized approach can shower away this type of problem.

CTEP, with PMB as a primary resource, developed a patient/caregiver education pamphlet for ad-hoc P&A of our IND agents. Its intent is to ensure stability-based dose uniformity and dose administration; to promote safe agent P&A; and to educate about proper disposal. All CTEP-sponsored pediatric trials and appropriate adult trials will include this pamphlet as an Appendix.

This pristine pamphlet is also posted on the CTEP web page as a template with unrestricted access. Any PMB customer who might not have time to develop patient instructions for agent P&A can simply download the form and complete it. Find the Patient/Caregiver Ad-Hoc Education Template at http//:ctep.cancer.gov under the CTEP Highlights, PMB, or Investigators Resources-Childhood Cancer Resources. An accompanying sample gives some advice about how to keep your site-specific instructions clean and crisp.

New on our web site: Patient/Caregiver Ad Hoc Education Template
http://ctep.cancer.gov/protocolDevelopment/patient_caregiver_education.htm

Recently Updated IBs

The investigator Brochures listed below were recently updated. The complete list of IBs is available on our web page at http://ctep.cancer.gov/branches/pmb/ib_current_electronic_list.pdf. Please send IB requests to ibcoordinator@mail.nih.gov.

Investigator Brochure Name	Size	Date Posted
330507 - 17-AAG (Tanespimycin) - 02-09 - Ver6.pdf	883 KB	02/10/2010
374551 - Fenretinide (capsules only) - 03-10.pdf	362 KB	04/06/2010
623408 - Chimeric Monoclonal Antibody 14.18 - 02-10.pdf	415 KB	03/02/2010
637037 - 06-Benzylguanine - 03-10.pdf	458 KB	03/23/2010
672423 - InterLEUKIN-12 - 03-10.pdf	500 KB	03/18/2010
683864 - CCI-779 (Temsirolimus) - A1012-09 - Ver13.pdf	3 MB	02/19/2010
683864 - CCI-779 (Temsirolimus) - Summary of Changes - 12-09 - Ver13.pdf	258 KB	02/19/2010
683864 - CCI-779 (Temsirolimus) - Summary of Changes - 12-09 - Ver13.pdf	496 KB	02/19/2010
707389 - E7389 (Halichondrin B Analog) - 12-09 - Ver7.pdf	1 MB	02/19/2010
729280 - Obatoclax MESYLATE (GX15-070MS) - 02-10 - Ver11.pdf	2 MB	03/12/2010
737754 - GW786034 (Pazopanib) - Summary of Changes - 02-10 - Ver7.pdf	34 KB	02/19/2010
737754 - GW786034-(Pazopanib) - 02-10 - Ver7.pdf	987 KB	02/19/2010
742460 - IMC-A12 (HuMAb IGF-1R; A12; Cixutumumab) - 01-10- ver6.pdf	1 MB	03/24/2010
749607 - MK-2206 -03-10 - ver3.0.pdf	987 KB	03/19/2010

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