

Recent Headlines in Clinical Research

Kathy Diener Dasse, PharmD, BCOP
December 5, 2006

Risk to Clinical Trial Subjects

- Review 3 cases of harm to subjects enrolled in early clinical trials
 - Review the responsibilities of various professionals involved in clinical research for the safety of the clinical trial subject
 - Evaluate risk to subjects enrolled in early phase clinical trials
 - Develop strategies for risk reduction in clinical trials and the role of the IDS pharmacist in the implementation of those strategies

Overview of Protection of Human Subjects

- Who is responsible for subject safety?
 - Government agencies
 - Advantage of seeing confidential or proprietary information
 - Institutional safeguards
 - The IRB and other review committees
 - The sponsor
 - The Investigator

Early Clinical Studies

- Methodology and Phase I Studies
 - Methodology Study Objectives
 - Gain a better understanding of a disease process
 - Phase I Objectives
 - Safety, tolerability, dose-finding, PK/PD
 - Only 11% of agents tested in Phase 1 clinical trials are registered due to
 - Toxicity of agent
 - Lack of efficacy
 - Both often use healthy volunteers
 - Advantage to use of healthy volunteers
 - AEs not confounded by pre-existing disease or concomitant medications
 - Clean PK/PD

Bhagal N. ALTA 2006;34:225-39. Kola I. Nature Rev; Drug Discovery 2004;3:711-5.

Early Clinical Studies

- Risk should be minimal with use of healthy volunteers
 - Methodology studies often involve "known" treatment modalities or procedures
 - Asthma methodology trial
 - Risk may be too great for healthy volunteers in Phase I studies for novel agents
 - Gene therapy for OTC deficiency
 - TGN 1412

Asthma Methodology Study

- "Mechanisms of Deep Inspiration-Induced Airway Relaxation"
 - Study Purpose: Gain a better understanding of airway hyper-responsiveness.
 - Methods: Healthy subjects were to inhale hexamethonium, a ganglionic blocker
 - Consent form described the drug as having been "used during surgery, as a part of anesthesia" and being "capable of stopping some nerves in your airways from functioning for a short period."
 - Risk section of the consent form noted that hexamethonium "may reduce your blood pressure..."
 - Consent form noted hexamethonium as being a "medication."

Steinbrook R. NEJM 2002;346:716-20.

Asthma Methodology Study

- Subject's Clinical Course:
 - May 4 – subject received 1 gm hexamethonium by inhalation
 - May 5 – cough develops
 - May 9 – subject is hospitalized with fever, hypoxemia, abnormalities on chest film
 - May 12 – progressive dyspnea develops. Subject is transferred to ICU
 - June 2 – subject dies as a result of progressive hypotension and multiorgan failure

Steinbrook R. NEJM 2002;346:716-20.

Asthma Methodology Study

- Follow-up
 - Institution suspends research involving healthy volunteers
 - Internal Review Committee Findings:
 - "study had solid scientific rationale and was well designed" and the use of hexamethonium was "scientifically sound."
 - The IRB was criticized for not requiring additional safety evidence for the use of hexamethonium.
 - Should the IRB have requested the investigator obtain an IND for the use of inhaled hexamethonium.
 - The investigator was criticized for not reporting symptoms of the first subject more promptly, for dosing additional subjects prior to resolution of symptoms in the first subject and for not understanding the potential for pulmonary toxicity due to hexamethonium.

Steinbrook R. NEJM 2002;346:716-20. Savulescu J. J Med Ethics 2002;28:3-4.

Asthma Methodology Study

- Follow-up
 - The FDA Review
 - Investigator was criticized for failure to submit an IND application prior to the start of the study and for failure to inform subjects that the use of hexamethonium by the inhalation route was experimental.
 - Review by the Office for Human Research Protections, et al.
 - Lack of comprehensive IRB review of new protocols
 - The External Review
 - Lack of comprehensive IRB review
 - Inadequate consent form
 - Inappropriate preparation of medication

Steinbrook R. NEJM 2002;346:716-20. Savulescu J. J Med Ethics 2002;28:3-4.

Asthma Methodology Study

- Recommendations
 - Additional resources/support for IRB
 - Includes increased support for literature searches
 - Investigators required to obtain written response from the FDA regarding the use of unapproved substances
 - Pharmacy has a greater role in the preparation of these substances

Steinbrook R. NEJM 2002;346:716-20.

Early Clinical Studies

- Risk should be minimal with use of healthy volunteers
 - Methodology studies often involve "known" treatment modalities or procedures
 - Asthma methodology trial
 - Risk may be too great for healthy volunteers in Phase I studies for novel agents
 - Gene therapy for OTC deficiency
 - TGN 1412

Gene Therapy

- Definition: a medical intervention based on modification of the genetic material of living cells
- Targeted diseases include cystic fibrosis, Alzheimer's Disease, Duchenne muscular dystrophy, hemophilia A, various cancers, SCID, and atherosclerosis

FDA Guidance for Human Somatic Cell Therapy and Gene Therapy, March 1998.
Steel M. JR Soc MED 2005;98:197-9. Selkirk SM. Postgrad Med J 2004;80:560-70.
Reid T. Cancer Research 2002;62:6070-9. Kohn DB. Nat Rev 2003;3:477-88.
<http://www.fda.gov/ldac/features/2000/gene.html>

Gene Therapy

- **Potential/theoretical toxicities/problems**

- Antigenicity
- Malignant transformation/inflammation
- Inefficient gene transfer
- Lack of transfer specificity
- Lack of long-term expression
- Difficulty in obtaining and maintaining primary cells ex-vivo
- Primary cells transferred to non-host tissue

FDA Guidance for Human Somatic Cell Therapy and Gene Therapy, March 1998.
Steel M. JR Soc MED 2005;98:197-9. Selkirk SM. Postgrad Med J 2004;80:560-70.
Reid T. Cancer Research 2002;62:6070-9. Kohn DB. Nat Rev 2003;3:477-88.
<http://www.fda.gov/fdac/features/2000/gene.html>

Gene Therapy

- **Study Rationale:** Current treatment for OTC deficiency has failed to impact the morbidity and mortality from hyperammonemic coma. Restoration of ornithine transcarbamylase (OTC) in the liver in subjects with OTC deficiency via adenoviral gene transfer therapy should normalize metabolism.
- **Methods:** Adenoviral gene transfer therapy for ornithine transcarbamylase (OTC) deficiency administered systemically

Raper SE. Molecular Genetics and Metabolism 2003;80:148-58.

Gene Therapy

- **JG's (subject 18) Clinical Course**

- Systemic inflammatory response syndrome, biochemically detectable DIC, multiple organ system failure leading to death at 96 hours post gene transfer

Raper SE. Molecular Genetics and Metabolism 2003;80:148-58.

Gene Therapy

- **Follow up:**

- FDA suspension of other trials involving infusing adenovirus into patients' liver
- Recombinant DNA Advisory Committee Meeting
 - Deaths of monkeys given high doses of a different modified adenovirus had not been reported
 - AEs in other subjects included liver toxicity
 - Although JG's ammonia level made him eligible for the protocol at enrollment, the level was elevated at the time of adenovirus infusion
 - Subject's bone marrow depleted of erythroid precursors

Beardsley T. Sci Am 2000;36-7.

Gene Therapy

- **Outcome**

- Increased Regulatory Scrutiny
 - Inspections
 - Development of Regulatory Guidances including a "Gene Therapy Monitoring Plan" Guidance and Monitoring for Delayed Adverse Events from the FDA
 - Implementation of Gene Therapy Patient Tracking System
- Research is ongoing

<http://www.fda.gov/cber/genetherapy/gttrack.pdf>
<http://www.fda.gov/cber/infosheets/genezn.htm>
<http://www.fda.gov/OHRMS/DOCKETS/98fr/05d-0310-gdl0002.pdf>
http://www.fda.gov/fdac/features/2000/500_gene.html

Gene Therapy

- **Recommendations**

- Balancing informed consent with harm to subject
- "Special Scrutiny" of protocols which study
 - Initial use of novel therapeutics
 - Unbalanced risk:benefit to subject
 - Ethical questions for which no precedent has been set

Savulescu J. J Med Ethics 2001;27:148-50.
Levine C. Ann Intern Med 2004;140:220-223

Early Clinical Studies

- Risk should be minimal with use of healthy volunteers
 - Methodology studies often involve "known" treatment modalities or procedures
 - Asthma methodology trial
 - Risk may be too great for healthy volunteers in Phase I studies for novel agents
 - Gene therapy for OTC deficiency
 - TGN 1412

"Superagonist" mAb

- Monoclonal antibody (mAb) therapy is NOT new
 - First mAb approved in 1986: muromonab (Orthoclone OKT3)
 - mAb therapy has inherent toxicities
 - Cytokine release syndrome has been seen with mAbs already approved
 - AEs controlled by slowing the infusion rate, changing the dose, or creating humanized antibodies
 - Most mAbs inhibit, not stimulate

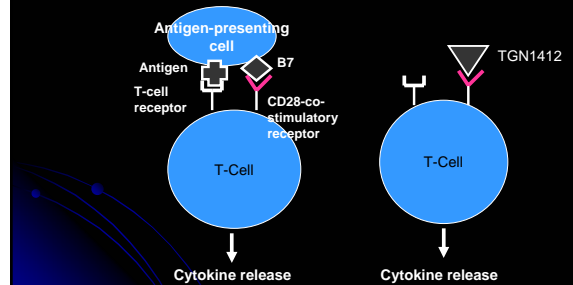
Tuma RS. J Natl Cancer Inst 2006;98:956-8

"Superagonist" mAb

- Study Rationale:
 - TGN 1412 was developed to "therapeutically balance the immune system in diseases associated with life-threatening abnormalities in T-lymphocyte number and/or function."
 - Potential uses in B-cell leukemias and in various autoimmune diseases.

http://www.mhra.gov.uk/home/idcplg?ldcService=SS_GET_PAGE&nodeId=433&within=Yes&keywords=TGN1412

"Superagonist" mAb



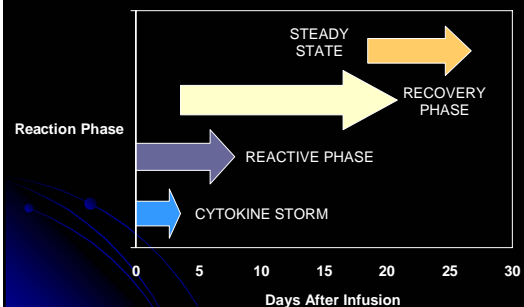
Bhogal N. ATLA 2006;34:225-39. Sharpe AH. N Engl J Med 2006;355:973-5.

"Superagonist" mAb

- Phase I, first in human, study
 - Objectives were safety and PK/PD
- Methods
 - 8 subjects per cohort (6 drug, 2 placebo) will be administered TGN 1412 as intravenous infusion at doses of 0.1, 0.5, 2 and 5 mg/kg body weight between the hours of 8 and 10 am.
 - Dosing rationale: 0.1 mg/kg dose represents a 500-fold safety margin with preclinical models
 - Criteria for dose escalation: Satisfactory review of safety data from at least 14 days following administration.

http://www.mhra.gov.uk/home/idcplg?ldcService=SS_GET_PAGE&nodeId=433&within=Yes&keywords=TGN1412

"Superagonist" mAb



Suntharalingam G. NEJM 2006;355:1018-28.

“Superagonist” mAb

- Follow-up
 - Investigations by MHRA
 - Events were not due to contamination, manufacturing problems or compounding errors
 - The protocol had been approved by 2 regulatory agencies and a local Ethics Committee
 - The trial was conducted per protocol.
 - TGN 1412 demonstrated “a pharmacological effect in man which was not seen in preclinical tests in animals at much higher doses.”

http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&useSecondary=true&ssDocName=CON2023822&ssTargetNodeid=389

“Superagonist” mAb

- Follow-up
 - The Expert Scientific Group on Phase I Protocols gave recommendations regarding
 - **Sharing information**
 - **Transition from preclinical to clinical development**
 - Evaluation of the use of relevant preclinical models to predict effect in humans
 - Dosing based on “minimum anticipated biological effect” instead of NOAEL
 - **Choice of subjects for Phase I studies**

http://www.dh.gov.uk/Consultations/ClosedConsultations/ClosedConsultationsArticle/fs/en?CONTENT_ID=4139038&chk=Heo5Fe

“Superagonist” mAb

- **Clinical environment of Phase I trials**
 - PI should be expert regarding the agent, its target and MOA
 - **Treatment strategies should be in place for potential adverse events (based on MOA)**
 - Clinical environment should include access to emergency medical equipment
- **Sequential dosing of trial subjects**
- **Communications with Regulators**
 - Developers should communicate early
 - Regulators should have access to independent experts
- **Skills and training of Phase I clinic personnel**

http://www.dh.gov.uk/Consultations/ClosedConsultations/ClosedConsultationsArticle/fs/en?CONTENT_ID=4139038&chk=Heo5Fe

“Superagonist” mAb

- Outcome
 - Regulatory effect on clinical trials not yet entirely evident
 - Other agents which stimulate T-cells are currently in trials
 - Ipilimumab (MDX-010) and ticilimumab (CP-675,206) are currently in Phase 3 trials for treatment of metastatic melanoma

Sheridan C. Nature Biotechnology 2006;24:475-6.

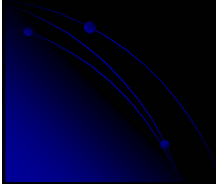
Summary – Gene Therapy and “Superagonist mAb”

- Recommendations
 - Understand the pharmacology of the compound being tested
 - Does the agent have a novel MOA?
 - Does the compound have available appropriate preclinical models?
 - Is there a plan in the protocol/IB addressing any potential adverse events based on the pharmacology of the compound?
 - Is it appropriate to test the agent in healthy volunteers or patients?
 - Establish clinic practices which optimize subject safety

Risk:Benefits for Healthy Volunteer Studies

- Pharmacists are in a unique position to add value to early phase and methodology studies
 - Understand pharmacology
 - Protocol review
 - Literature searches
 - Understand potential adverse events
 - Insure appropriate monitoring is in place
 - Plan for potential adverse events should be available in IB or protocol
 - Control of drug material

Questions



Tools for dispensing and accountability of investigational drugs

December 5, 2006

- Rivka Siden, MSc, Pharm.D.
- University of Michigan Health-System and College of Pharmacy

Discussion topics

- Creating uniform approach
 - Dispensing
 - Prescribing
 - Opening a study
 - Inventory management
 - Document retention
- Handling audits
- Preparation of budget

The University of Michigan Hospitals and Health-Centers

- Tertiary care facility
- 865 inpatient beds (adult, children, neonates)
- 30 health centers and 120 clinics
- General Clinical Research Center
- Specialty care: cardiovascular center, comprehensive cancer center, six disease management programs, eye center, aging center, diabetes, stroke, transplant, trauma burn, women health...

The University of Michigan Investigational Drug Service

- ~280 open protocols
- Review ~16 protocols per month
- Open ~13 protocols per month
- 3.4 FTEs of pharmacists (↑ by 0.6 FTE)
- 4 FTEs of technicians
- Currently organized in pharmacist-tech teams

Dispensing areas

- IDS pharmacy (outpatient clinics)
- Inpatient satellites (adults/children)
- Operating room
- Cancer center infusion pharmacy
- Cancer center outpatient pharmacy
- Both IDS staff and pharmacy staff involved in dispensing

Life cycle of a protocol

- Review prior to IRB submission (eReserach)
 - Acknowledgement and preparation of budget
- IRB approval and contract
- Site initiation
 - Dispensing guidelines
 - Pharmacy worksheets (if needed)
 - Template of the prescription

Life cycle of a protocol

- Receipt of drug
 - Opening of study specific notebook
 - Entering into IDS computer program for dispensing, billing, workload (Web-IDS)
 - Entering into Omnicell PharmCentral
 - Template of label in hospital computer system (if satellite dispensing)
 - Accountability logs

Life cycle of a protocol

- Processing drugs that are returned from subjects
- Monitor visits
- Inventory management
- Billing
- Internal audits
- External audits
- Closeout and archiving

Regulations for management of Investigational Drugs

- Good Clinical Practice (GCP) Guidelines
- Code of Federal Regulation (CFR)
- JCAHO
- State and Federal law
- Institutional policies

Dispensing Guidelines

- Summary of the protocol, Investigator's Brochure and pharmacy binder
- Educational tool for pharmacy staff, nursing and study staff
 - Practical guide for dispensing pharmacists
 - Information for the IDS staff on specific study requirements (accountability records, ordering drug, drug returns)

Dispensing Guidelines - Background

- Study staff (PI, Co-I, coordinators, data managers, study nurses, IDS staff)
- Information on the disease and study rationale
- Summary of the study design, treatment plan, drug administration
- Drug information including MOA, expected adverse effects, potential drug interactions, and pharmacokinetics
 - For non FDA-approved drugs- summary of information from the protocol and the Investigator's Brochure
 - For FDA-approved drugs-refer to the drug package insert

Dispensing Guidelines- Dispensing Instructions

- Drug location and storage condition
- Patient location and urgency of dispensing (cath lab vs outpatient prescription)
- General supply vs patient specific supply
- Drug description (strength, packaging)
- Patient registration and randomization instructions, instructions on use of IVRS (if pharmacy randomize)

Dispensing Instructions

- Dose
 - Frequency and duration of treatment (length of cycle, number of cycles)
 - Weight/BSA based dosing (TBW vs IBW)
 - Dose reductions

Dispensing Guidelines-Dispensing

- Compounding directions for injectables, oral liquids:
 - Diluent, container (non-PVC) concentration, storage after dilution
 - Stability (expiration of reconstituted vial vs diluted solution for administration)
 - Tear off labels
 - Handling used vials

Dispensing

- Dispensing pre-filled units, drug bottles
 - Dispensing in original container or counting out into a prescription bottle
 - Is a container provided?
 - Tear-off labels
 - Handling unused drug (at the end of the study/expired drug)
 - Handling returns from patients (NCI, investigator-initiated, industry)
 - Compliance (diaries, pill count)

Investigational drugs DO expire!

- Why a date is not provided?
- Expiration date vs re-test date
- Where to find expiration/re-test dates?
- Extensions of dates

Dispensing Guidelines-Administration

- Administration instructions
 - Premedications
 - Injectables
 - Route and rate
 - Flushing
 - Monitoring
 - If multiple drugs- order of medications and time line
 - Oral
 - Food and food interaction (grapefruit)
 - Instructions to minimize risk (exm. upright position)
 - Order of medications and time line

Template of the label

- Follow state requirements
 - Patient name vs initials
- List auxiliary labels
- Satellite computer code (provide on prescription; especially important if same drug in multiple protocols)
- Example

The University of Michigan Hospitals and Health Clinics
 Ambulatory Care Pharmacy
 1500 East Medical Center Drive
 Ann Arbor Michigan, 48109
 Phone: 736-936-8210

Patient name: _____ Rx # _____
 Dr: _____ Date: _____

Randomization number: _____

Bottle 1 / Bottle 2

Take TWO capsules from BOTTLE 1 and TWO capsules from BOTTLE 2 twice a day for three days. Take the first dose 30-60 minutes before chemotherapy. Return used and unused drug bottles to clinic. Drug X 250mg/placebo capsules-12 capsules.

Protocol # UMCC 2006.0202

Expiration date: **Pharmacy: Give both bottles the same expiration date**

Store at room temperature.
 Investigational drug

Dispensing Guidelines- Study Managements Section

- Accountability logs-sponsor, site, NCI
- Drug ordering (minimum reorder levels)
- Processing shipments (temp sensors)
- IVRS information
- Monitor information
- Drug return/disposition information
- Billing Information

Worksheets

- For studies that require multiple dilutions, complicated calculations, overfill for priming tubing
- Pharmacy section is added to the prescription or IDS provides a calculation sheet
- Some sponsors require the use of a calculation sheet

Pharmacist Worksheet-University of Michigan

Protocol No: UMCC 2001-101

Protocol Title: The pharmacokinetics of ganciclovir in BMT subjects with GVHD

Subject # _____ Subject Initials: _____

- a. Subject Weight (kg): _____
- b. Dose of IV ganciclovir (5 mg/kg): _____ mg
- c. Calculate the desired concentration. For wt<100kg use 50mL, for wt≥100kg use 100mL. Infusion concentration should not exceed 10mg/mL.
 Desired concentration = Dose (b) _____ mg ÷ $\frac{\square \text{ Stud.}}{\square 100\text{ml}}$ = _____ mg/mL (d)
- e. Total Volume of Infusion $\frac{\square \text{ Stud.}}{\square 100\text{ml}}$ + 25 mL = _____ mL (e)
- f. Amount of ganciclovir needed =
 Desired concentration (d) _____ mg/mL X total volume of infusion (e) _____ mL = _____ mg (f)
- g. Pick a 500mg ganciclovir vial(s) from the box that is assigned to the patient. Reconstitute the vial with 10 mL of Sterile Water for Injection, USP, which yields a 50 mg/mL solution of ganciclovir.
 1. Shake the vial to dissolve the drug. Typically, reconstitution takes less than 1 minute, though it may take up to 3 minutes.
 2. Inject the reconstituted solution for any particulate matter or discoloration. If any particulate matter or discoloration is observed, do not use the vial.
 3. Due to the possibility of crystal formation, the contents of the reconstituted vial should be used immediately. **Do not refrigerate.**

- h. Volume of ganciclovir needed =
 Amount of ganciclovir needed (f) _____, 50 mg/mL = _____ mL (h)
- i. Volume of 0.9% Sodium Chloride Intravenous Solution, USP needed
 Total volume of Infusion (e) _____ - Volume of ganciclovir (h) _____ = _____ mL (i)
- j. Inject ganciclovir solution 50mg/mL (h) _____ mL of into an empty Vialflex bag;
- k. Inject 0.9% Sodium Chloride Intravenous Solution, USP (i) _____ mL of to achieve the Total volume of Infusion (e).
- l. Refrigerate. The expiration of the solution for infusion is 24 hours in the refrigerator.
- m. Attach tubing and prime it. Fill a sponsor provided yellow label with the volume to be infused that you picked in (d) (50mL for wt<100kg and 100mL for wt≥100kg) and label the bag. In addition label the bag with the following label:

Rx # _____ Date: _____ Dr: _____
 Name: _____ CPT: _____
 Infuse only _____ mg (_____ mL) IV via infusion pump over one hour between 7 a.m. and 9 a.m. within 10 minutes of finishing breakfast as directed by protocol. At the end of the infusion, do not flush tubing. Attached tubing is primed
 Bag contains overfill:
 Ganciclovir injection study drug in 0.9% NaCl, TV: _____ mL
 Protocol: UMCC 2001-101
 Investigational drug
 Expiration date and time: _____ (24 hrs ref)

Auxiliary labels: Chemo precautions, Keep refrigerated

n. Sign the vial(s) out of the patient specific in ventory.
 Tech Signature _____ Date/Time _____
 Pharmacist Signature _____ Date/Time _____

Prescribing

Drug X outpatient study

- Drug X for treatment of chemo-induced nausea and vomiting
- Randomized and blinded
- Stratification for use of aprepitant (Emend)
- 1000mg/day, 2000mg/day, placebo for three days divided BID

<Name and address of the institution>
 <Study Name>
 Study number: UMCC 2006.0202
Outpatient prescription

Visit date: _____ Fax prescription to: XXX-XXXX
 Pick up date and time: _____

Subject Name: _____
 Institution Registration number: _____
 Is the patient taking aprepitant (Emend)? (Please circle one): YES NO

Subject Study Number: ***
 *** Subject Study # will be 02 -1##-HT if the subject is NOT taking Emend.
 Subject Study # will be 02 -2##-EM if the subject IS taking Emend.

Dispense:
 Drug X 250mg or placebo according to the study randomization code
Dose: Drug X 1000mg/day or Drug X 2000mg/day or placebo.
Quantity: Bottle 1-12 capsules; Bottle 2-12 capsules

Sig: Take TWO capsules from BOTTLE 1 and TWO capsules from BOTTLE 2 twice a day for three days. Take the first dose 30 to 60 minutes before chemotherapy. Return used and unused drug bottles to clinic.

Contact name: _____ Phone: _____

Authorized prescribers: <insert names of authorized prescribers at the site and their doctor number, phone/pager number>

Dr. _____ Dr. No. _____ Date: _____
Print Name/Sign

With questions, call the Pharmacy (XXX-XXXX) M-F 8:00AM to 4:30PM

UNIVERSITY OF MICHIGAN HOSPITALS AND HEALTH CENTERS
 1500 East Medical Center Drive, Ann Arbor, MI 48109 734.936.4000

DRUG ORDER FORM-EXAMPLE

DIAGNOSIS: Breast cancer ALLERGIES: _____ BIRTHDATE (MM/DD/YY): _____
 NAME: _____
 CPH #: _____

PROTOCOL NUMBER or NAME (required): UMCC 2006.0201 GENDER: M F
 CYCLE # ____ of ____ (if applicable) VISIT NO: _____
 Does this investigational Drug Service provide any drugs? Yes X No _____

HEIGHT: cm WEIGHT: kg BSA: NA m² IV Access Device Name: _____
 # units: _____
 Is the patient diabetic? Yes ___ No ___
(required for Home Care patients)

AGE: _____ Creatinine clearance (required): _____ Other information used for dose calculation: See table below
Use TW and Cockcroft-Gault formula

HOLD CHEMOTHERAPY FOR THE FOLLOWING PARAMETERS:
 For an increase in serum creatinine ≥0.5mg/dL from normal baseline creatinine or ≥1mg/dL from an abnormal baseline creatinine, hold and callpage the PANP
 Baseline Creatinine: _____mg/dL. Please mark: Normal/ Abnormal

ARM 1: Zoledronate
 Fax prescription to CGC infusion pharmacy (_____) Medication Timing: _____

Start Date: _____
 Patient study number: _____
 Note! Drug cannot be dispensed without the patient study number.

Dispense:
 Zoledronic acid STUDY DRUG _____ mg* in 100mL 0.9% Sodium Chloride on:
 * see table for dose adjustments

Baseline Creatinine Clearance (mL/min)	Zoledronic Acid (mg)
≥50	4
30-49	3
10-29	1.5
≤9	0

Sig: Infuse entire contents of bag IV over at least 15 minutes.
 Pharmacy: Use IDS supply for UMCC 2006.0201. DIGI code ZOLED201

Authorized prescribers: (Name/pager): _____
 by: _____/page: _____
 Study staff: _____ RN, Study nurse/pager

PRESCRIBER SIGNATURE/PRINTED NAME: _____ PAGER #: _____ DATE/TIME: _____
 Last reviewed on: _____ by: _____

Using preprinted medication order forms to improve the safety of investigational drug use.

Tamer HR and Shehab N.
Am J Health-Syst Pharm. 2006;
 63:1022-8.

Checklist for opening new studies

- Creating a study notebook-uniform format
- Obtaining IRB approval document
- Creating a computer file
- Collecting account numbers for billing
- Example

Investigational Drug Service Checklist for New Studies

Study Drug Name: _____ Protocol Number: _____ HUM # _____

Date Study Opened or Date Drug Received: _____

1. **Study File:** Get the hanging file. If you cannot locate file, check "New Protocol Review List" ask pharmacist.
2. **Notebook:** Prepare notebook with following sections and related documents:

Correspondence (communication sheet on top, letters, citations notices & email)	Drug Data (Package Insert, MSDS, & Certificate of Analysis)	Invoice Packing Sheets
IVRS (Use Instructions)	Dispensing Guidelines	Ev Order Drug (Form)
IDS Acknowledgment/Consent/Research sections (15-1, 15.1, 2 for checklist for non-research studies)	Prescription template	Drug Return to Company/ Drug Destruction on Site
Fee sheet/billing information	Master Log/randomization code	Monitor Vials and Assays (include blank vials checklist)
IRB Approval (or request letter)	Inventory (different sections for bulk drug, each drug, each strength, sponsor-provided forms, IDS forms, patient-specific forms and from Blank Inventory Sheets)	Large envelope for Prescriptions
Digi Formulary Request Label	Sample Inventory Sheets (if needed)	Other/Misc (workbooks, special forms)
3. **Receipt of Drug:** When IDS receives drug, record it on the "Drug Rec'd Sheet" located on the rolling shelves.
4. **Invoice:**
 - a. Verify that drug received matches invoice, rectify if needed.
 - b. Sign and date invoice after verification.
 - c. Acknowledge through IVRS website, fax, etc as required by sponsor
 - d. Fax copy of invoice to study coordinator if required
 - e. Label all received product with drug name, protocol #, and any other required identifiers
 - f. Place invoice (or copy) in "Invoice" section of study notebook
5. **Inventory:** Prepare appropriate inventory sheets (IDS-prepared or sponsor-provided) with all header info filled out and log drug onto the sheet (photocopy several sheets that contain the header for future use).
6. **MRL:** Establish with RPh for drug inventory & record on upper right corner of inventory sheet
7. **Billing:** Determine if short code information has been obtained. If not,
 - a. Request (via email) that the study coordinator/administrator complete a Billing Information Sheet and return to IDS.
 - b. Place documentation of request in "Fee Worksheet/Short Code" section of the study notebook.
 - c. Once completed Billing Info Sheet is received, place in "Fee Worksheet/short code" section of notebook.

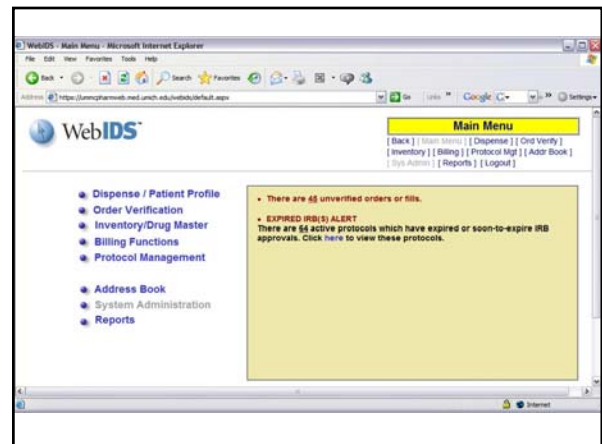
NCI inventory sheet

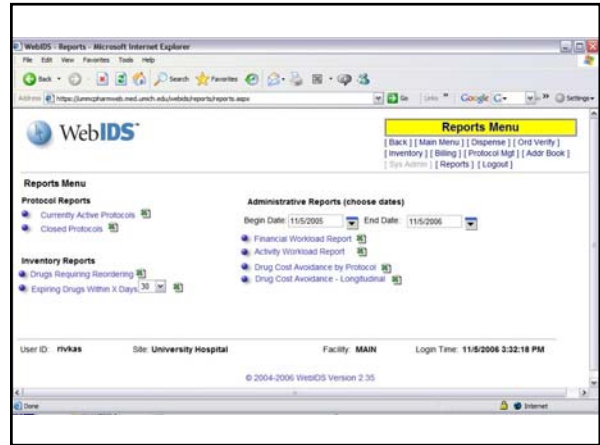
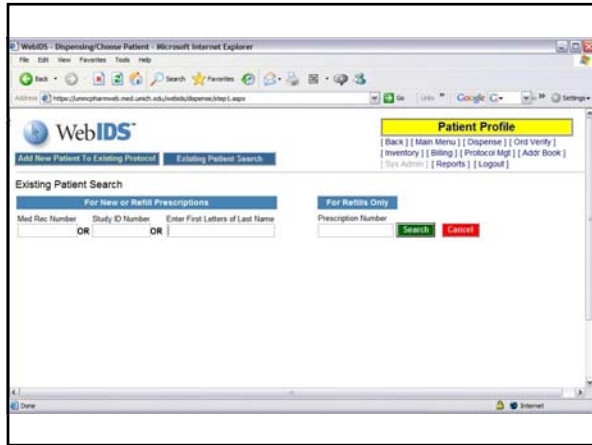
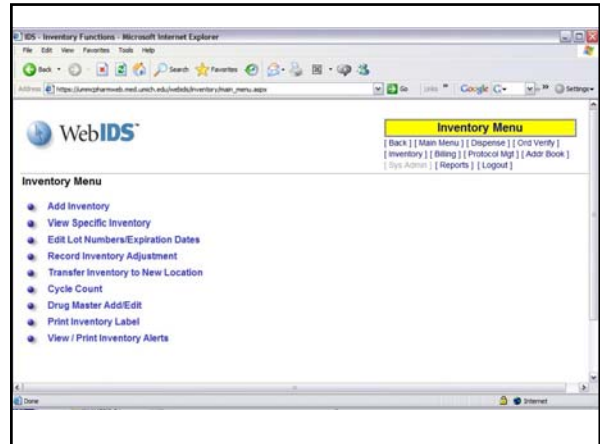
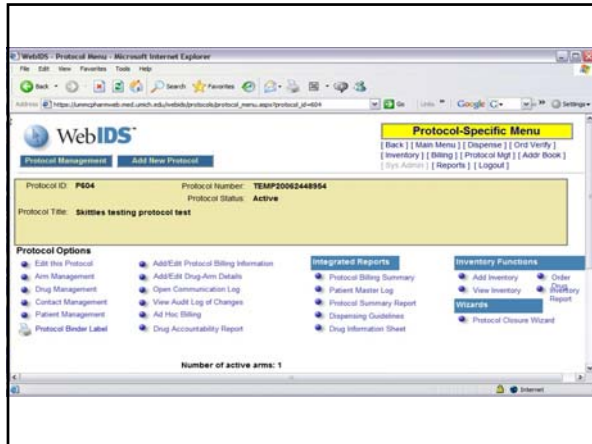
National Institutes of Health National Cancer Institute		Division of Cancer Treatment and Diagnosis Cancer Therapy Evaluation Program		PAGE NO. CONTROL RECORD X SATELLITE RECORD				
Investigational Agent Accountability Record		NCI Protocol No. 0406 JMI Study number: GCRC 0006		Dose Form and Strength: 500mg capsules /35 caps per bottle				
Name of Institution: University of Michigan Hospitals and Health Centers		Agent Name: AZ101		Dispersing Area: IDS				
Protocol Title: Phase IA trial of AZ101 in patients with prevalent subclinical neoplastic lesion		Investigator Name: Dr. _____		NCI Investigator No.: _____ Expiration: _____				
Line No.	Date	Patient's Initials	Patient's ID No.	Dose	Quantity Dispensed or Received	Balance Forward	Manufacturer and Lot No.	Receiver's Initials
1.						Balance		
2.								
3.								
4.								
5.								
6.								
7.								

- ## Accountability
- Physical inventory- at least quarterly
 - Keep all invoices
 - Keep records of drug returns
 - Keep records of drug transfers (if allowed)
 - Keep records of destruction on site
 - Keep records of disposition of unused drug that is returned for patients

- ## Computer programs to support IDS
- Goal: Program for inventory management, labels, and billing
 - Literature review
 - Study and drug information
 - Patient data (CRF)
 - Accountability (Excel, Access)
 - Labels generation (Existing inpatient or outpatient systems)

- ## Web-IDS
- Conflict of interest
 - Poster presentation at the 39th Annual ASHP Midyear Clinical Meeting, Orlando, FL.
 - McCreadie, SR. McGregory, M. Siden, R. Tamer, H. Sweet, B. et al. **Development of a custom information system for an investigational drug service.** [Abstract of meeting presentation. Journal article] *Ashp Midyear Clinical Meeting*. 39(DEC): p P362D. 2004.





Record retention

- 21 CFR 312.57 c
 - A sponsor shall retain the records and reports for 2 years after a marketing application is approved for the drug; or, if an application is not approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and FDA has been so notified.

**Investigational Drug Service
STUDY CLOSE OUT PROCEDURES CHECK OFF LIST**

Drug/Protocol Name _____
Box# _____

Protocol# _____ Close Out Date _____

1. Before a monitor comes to close out a study OR when we receive notification from a company that a study is closed, get protocol file, get drug and inventory sheets and any related information for that study from satellite areas. Look on IDS-B2 inventory sheets to determine where drug was sent. Write "returned to IDS" on satellite inventory sheet and write "rec'd from Pharmacy" on IDS-B2 inventory sheet.
date _____ initials _____

2. Count all dispensings on Satellite inventory sheets and IDS inventory sheets (check off with a red pen) and write the number in the Quarterly Report Billing Book.
date _____ initials _____

3. Pull unused drug from inventory. Check on IDS-B2 inventory sheets if any unused drug was previously pulled from stock and placed on our expired drug/return shelves. Also check these shelves for any used drug (drug that was returned by the patient). If the sponsor does not have a special form for returning used or unused drug, use our form. Write "Returned to Company" on IDS inventory sheets and zero out the balance.
date _____ initials _____

4. Obtain information on where drug should be sent. Return all drug. Be sure you make a copy of all return forms for our file.
date _____ initials _____

5. Clip together all scripts for the study and place a tag on the scripts that states "destroy after (date 6 years from close out)." File scripts.

date _____ initials _____

6. WEB IDS CLOSE OUT WIZARD:

date _____ initials _____

6. DELETE the drug from DIGI (a pharmacist will show you how to delete from digi in the shared drive under "digi formulary").

date _____ initials _____

7. File this check-off sheet in "close-out" notebook.

date _____ initials _____

8. Tear down notebook (remove dividers) and place all notebook information in file. Place file in the storage file box for closed studies. Update the "close out transferred" file in the IDS shared drive (see "closed file storage procedure").

date _____ initials _____

s:\ids\closeout.doc

Good Clinical Practice and the Code of Federal Regulations

- All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification
- Quality assurance of every aspect of the trial should be implemented

Audits

21 CFR 312.68

An investigator shall upon request from ...[the] FDA, at reasonable times, permit such officer or employee to have access to, and copy and verify any records or reports made by the investigator

The investigator is not required to divulge subject names unless the records of particular individuals require a more detailed study of the cases, or unless there is reason to believe that the records do not represent actual case studies, or do not represent actual results obtained.

Audits

- Tour of the facility to ensure that drugs are stored under the appropriate conditions (temperature/locked)
- Tour of the satellites
- Documents that are reviewed:
 - Inventory records (including physical inventory)
 - Invoices
 - Return/destruction/transfer
 - Expiration information or relevant communication on expiration
 - Dispensing guidelines, study patient list, other documents do not need review

Check list for preparation for audits

- Siden R, Tankanow RM, Tamer HR. Understanding and preparing for clinical drug trial audits. *Am J Health-Syst Pharm.* 2002; 59:1301-8.

University of Michigan Health-System
Department of Pharmacy Services
Investigational Drug Service

AUDIT CHECKLIST

Drug name _____ PROTOCOL # _____

Audit Date _____ Audit Company _____

Principal Investigator _____

Data manager: _____ Phone: _____

____ Gather the pharmacy file, notebook and records pertaining to the above protocol.
 ____ If the study is closed, obtain the closed file.
 ____ If the study is open, obtain the current inventory records from Satellites. Perform an inventory count and leave a new inventory sheet at the satellite.
 ____ Sort invoices by date
 ____ Sort Central and Satellite inventory records by location and date
 ____ Sort return forms by date
 ____ Sort transfer forms by date
 ____ Sort all other records by date (Example: randomization information, worksheets)

____ Check that all invoices were signed in on the Central inventory sheet (make sure lot #s and expiration dates are on sheet)

____ Check that all returns were signed out of the Central inventory sheet

____ Check that all transfers were signed in or out of the Central inventory sheet (for sponsors that allow transfers between protocols, be sure a transfer form was filled out)

Continue on the next page

_____ Check the Central inventory sheets against Satellite inventory sheets. Was everything logged in and out correctly? (check that dates match and lot #s and quantities match)
 _____ Was Central inventory sheet filled out properly?
 _____ Was the top of the inventory sheet including page #s filled out?
 _____ Were all entries filled out properly? Check for the following:
 _____ Patient initials (not name)
 _____ If the study requires a patient study identification number on the inventory sheet, check that the number is filled and is correct
 _____ The dose and frequency of administration
 _____ Initials of recorder and pharmacist
 _____ Lot number and expiration dates
 _____ Was Satellite inventory sheet filled out properly?
 _____ Was the top of the inventory sheet including page #s filled out?
 _____ Were all entries filled out properly? Check for the following:
 _____ Patient initials (not name)
 _____ If the study requires a patient study identification number on the inventory sheet, check that the number is filled out and is correct
 _____ The dose and frequency of administration
 _____ Initials of recorder and pharmacist
 _____ Lot number and expiration dates
 _____ Perform an inventory in the JDS Central area. Make sure that the book inventory matches the shelf. If not, try to resolve the discrepancy by checking the math, comparing prescriptions to inventory records, and consulting with the individuals who dispensed the drug.
 _____ For closed studies, verify that all drug was returned/transferred/discarded and records that indicate the disposition are available.
 Remember: Ditts marks are not allowed on accountability records. Only use black pen. Do not use correction fluid. Make corrections by putting a single line through the item and writing in the correct item. Initial and date the correction.
 List issues that require further investigation/intervention by the audit coordinator:

 Initial preparation of file: _____ Name _____ Date _____
 Reviewing pharmacist: _____ Name _____ Date _____

Pharmacy charges

- Start up fee
- Ongoing maintenance fee
- Dispensing and compounding fee
- Other fees: storage, closeout, monitor visits, audits, counting returns, product destruction, transfer to other sites, IVRS, mail out (plus carrier cost), controlled substances fee, transfer to another site

Pharmacy charges-UM

- Opening and closing a study- \$ _____
 - Review of study and identification of pharmacy issues
 - Initial receipt and inventory of investigational agent(s)
 - Preparation of Drug Accountability Records /Notebook
 - Development and distribution of dispensing guidelines, including randomization and double blinding, if requested
 - Staff in-services.
 - Meeting with investigators and study monitors
 - Study termination, reconciliation of drug accountability records, photocopying, return of drug, maintenance of discontinued study file

Pharmacy charges

- Dispensing cost
 - Different charge according to preparation
 - Oral medication, injectables, capsule preparation
- Study Maintenance \$____/month
 - Physical inventory
 - Ordering and maintaining appropriate stock of drug
 - Checking for expired drugs; date extensions and re-labeling of drugs when necessary.
 - Monitor visits.
 - Internal QA audits.

Pharmacy charges

- Counting/Disposition of Drug Returns \$____/tech hr
Hourly fee for counting
- Clinical Services \$____/pharmacist hr
 - Patient monitoring activities (blinded studies)
- Other: drug cost
- Charges are for time and supplies-no profit

Pharmacy budget

- Institutions have different items but most use same components
- Different fees for industry sponsored, investigator-initiated, cooperative groups
- Cooperative groups-salary support
- Blanket support to cover workload



Things to remember...

- Managing investigational drug studies is a complex and detailed process
- Heavily regulated and audited
- Key for success:
Templates of prescriptions, pharmacy guidelines, templates of labels and inventory records

Issues Related to Dispensing Investigational Drugs

Helen R. Tamer, Pharm.D.
University of Michigan Health System
University of Michigan College of Pharmacy
Ann Arbor, MI
December 5, 2006

Issues Related to Dispensing Investigational Drugs

- Drug Supply Issues
- Dispensing drug from areas outside of the Investigational Drug Service
- Compounding specialized dosage forms for investigational use

Drug Supply Issues

How can IDS ensure that authorized persons are requesting drug for study subjects?

- GCP Consolidated Guidelines
- Cancer Therapy Evaluation Program (CTEP)
- PI authorization (list)
- Protocol-specific prescription templates

Drug Supply Issues

How can IDS ensure the correct study supply is being dispensed (same drug used in multiple studies or study supply is a commercially available drug)?

- Labeling (protocol number)
- Designated storage area
- Educate staff (re: study, subject clinic date)
- Protocol-specific prescription template

Drug Supply Issues

How can IDS manage protocol amendments involving drug dose or dispensing?

- System to receive the amendment
- Dispensing guidelines
- Education
- Protocol-specific prescription template

Drug Supply Issues

Does IDS need to handle alternative products/herbal supplements used in human subject research?

- MAYBE

Drug Supply Issues

Per JCAHO: medication includes prescription meds, sample meds, herbal remedies, vitamins, nutraceuticals, OTC meds, vaccines, diagnostic and contrast agents, used on or administered to persons to diagnose, treat or prevent disease or other abnormal conditions; and any product designated by the FDA as a drug.

Drug Supply Issues

According to Section 201 (g) (1) of Federal Food, Drug and Cosmetic Act (21 USC Section 321), drugs are defined as (B) articles intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in man and (C) articles (other than food) intended to affect the structure or any function of the body

Drug Supply Issues

Does IDS handle?

- JCAHO or FDC Act definitions
 - Study intent
- IND necessary?
 - If yes, then considered a drug
 - IDS handles
 - Certificate of Analysis (purity; meeting USP stds; consistency)
 - Informed consent (not FDA regulated or approved)

Drug Supply Issues

Examples:

- Hawthorn for the treatment of CHF
- Ginger for the treatment for chemotherapy-induced Nausea and Vomiting
- Stri-Vectin molecular and histological effects on photodamaged skin
- Protandim effect on antioxidant enzymes in red blood cells and skin

Issues Related to Dispensing Investigational Drugs

- Drug Supply Issues
- Dispensing drug from areas outside of the Investigational Drug Service
- Compounding specialized dosage forms for investigational use

Dispensing from areas outside of the IDS

In our institution, most dispensing (inpt and outpt) is completed by IDS staff, some by inpt and outpt satellite pharmacy staff—how does IDS control inventory in the pharmacy satellites?

- Education/in-service
- Dispensing guidelines
- System in place to supply satellite
- Monitor supply/accountability logs
- Dedicated space in satellite for storage

Dispensing from areas outside of the IDS

My IDS is housed in a Univ. Hospital; the hospital has off-site outpt clinic areas. How does IDS handle dispensing for a study when the study subjects are off-site?

- JCAHO (MM#1-20) requires that when pharmacy services are provided, the pharmacy controls the storage, dispensing, labeling and distribution of the investigational drug.
- ASHP recommends Investigational Drugs be handled by pharmacy

Dispensing from areas outside of the IDS

Off-site options:

- IDS dispenses, utilize delivery services to take to off-site clinic
- IDS dispenses, having study staff pick up and take to off-site clinic area

Dispensing from areas outside of the IDS

Occasionally, studies require immediate administration of or accessibility to the investigational drug to ensure adherence to trial methodology. How does IDS maintain oversight when drug is handled by PI, not IDS?

- Drug received, stored and dispensed by PI in area other than the pharmacy, usually close to where subjects will be administered drug

Dispensing from areas outside of the IDS

PI Request of IDS waiver

- Opportunity for IDS pharmacist to review study
- Determine whether IDS can safely allow PI to store/dispense drug (w/o IDS involvement)

Dispensing from areas outside of the IDS

IDS waiver criteria

- Remote site (with time constraints--IVRS)
- Unpredictable timing, immediate/emergent drug administration (ER)
- Short stability times require preparation immediately before administration (OR)
- Contrast agents (normally managed by Radiology Dept, with pharmacy inspection)
- Non-IDS pharmacist takes responsibility (RPh is co-I)
- Not a special study supply (use hospital supply but bill study acct)

Dispensing from areas outside of the IDS

IDS waiver permitted

- PI must comply with state and fed law
- Locked, limited access area
- Sample label that will be affixed to drug
- MD dispensing license (MI req, outpt use)
- IDS may assist PI by providing sample label, DG, sample accountability log
- Audit/inspection by IDS

Dispensing from areas outside of the IDS

IDS Audit of “waived” studies

– Audit checklist used to verify

- Drug storage/facility conditions
- Drug inventory (accountability) records
- Drug labeling
- Drug information

University of Michigan Health System Department of Pharmacy Services
Investigational Drug Service

Audit Form for the Inspection of Investigational Drug Storage/Dispensing Areas Outside of Pharmacy

Department Audited: _____ PI Name: _____
 Study Title/Protocol #: _____
 RH #: _____
 Drug Name: _____
 Audit Date: _____ Auditor Name: _____

I. Drug Storage Conditions

- ___ Drug inaccessible to unauthorized personnel
- ___ Required temperature
- ___ Temperature (room, refrigerator or freezer) log available
- ___ Spoiled items not stored with drugs
- ___ Drug containers appropriately labeled with drug name/protocol number
- ___ If required, drug protected from light
- ___ Drug not expired

II. Drug Inventory (Accountability) Records

- ___ Invoices available
- ___ Name/strength of drug recorded
- ___ Lot numbers recorded
- ___ Date received, dispensed, returned/dispensed recorded
- ___ Amount received, dispensed, returned/dispensed recorded
- ___ Subject name or initials recorded
- ___ Subject study number recorded
- ___ Initials of receiving/dispensing physician recorded
- ___ Dose recorded
- ___ Periodic inventories performed
- ___ Only black pen used, correction made by single line through item
- ___ Drug on shelf matches drug inventory listed in the record

III. Drug Labeling (examine drug return or sample label)

- ___ Dispensing physician name, address and phone number
- ___ Drug name/strength
- ___ Subject name
- ___ Date dispensed
- ___ Instructions for use
- ___ Auxiliary label-pretention
- ___ Auxiliary label indicating "For Investigational Use only"
- ___ Quantity dispensed
- ___ Expiration date

IV. Drug Information

- ___ Dispensing information available
- ___ Drug information available
- ___ Protocol available

V. Other

- ___ IRB approval/renewal letter in study file
- ___ Dispensing physician's Drug Control License available
- ___ Subject signed consent form available
- ___ Documentation in chart/study record of subject receiving invest. drug

Study Department Personnel Reviewing Audit: _____ Date: _____

Issues Related to Dispensing Investigational Drugs

- Drug Supply Issues
- Dispensing drug from areas outside of the Investigational Drug Service
- Compounding specialized dosage forms for investigational use

Compounding Specialized Dosage Forms for Investigational Use

Our IDS has been asked to compound a product for a study—can we do this?

FDA Compliance Policy Guide on Pharmacy Compounding (Sec 460.200)

Can:

- Reasonable quantities upon receipt of valid prescription from licensed practitioner
- Limited quantities in anticipation of prescription
- Use quality drug substances

Cannot:

- Drugs that were withdrawn from market for safety reasons
- Without IND, if active ingredient not component of FDA-approved drug
- Copy commercially available FDA-approved drugs
- Compound for third parties for resale to pts

Compounding Specialized Dosage Forms for Investigational Use

Consider/evaluate:

- Published data
- Appropriateness of ingredients
- Route of administration
- Risk vs. benefit
- Toxicities
- Contaminants
- Available resources (space, equipment, personnel)
- USP 795, USP 797, USP 1075

Compounding Specialized Dosage Forms for Investigational Use

Our IDS has been asked to prepare capsules from a raw chemical/substance—can we do this?

USP 1075 : USP- or NF-grade substance prepared by manufacturer registered with the FDA preferred (pharmaceutical grade)

Compounding Specialized Dosage Forms for Investigational Use

The only substance available for compounding is not “pharmaceutical grade”—can we use it?

USP 1075:

- High quality source: analytical reagent grade, American Chemical Society certified or Food Chemical Codex grade
- Assess purity and safety (evaluate Certificate of Analysis); reliability and reputation of source

Compounding Specialized Dosage Forms for Investigational Use

A PI has asked our IDS to prepare a sterile product from a raw chemical (non-sterile powder) for a study--can we do this?

- HIGH risk compounding per USP 797
- Consider preparing small batches that can be sterilized and tested for stability and sterility

Compounding Specialized Dosage Forms for Investigational Use

A PI has contacted me to prepare blinded capsules using a manufactured, FDA-approved drug for a study—what are my options?

- Tablet/capsule within opaque cap; crush tablet, mix with lactose then place in opaque cap
 - Beyond-use dating (USP 795), stability testing, small batches
- Compounding pharmacy
- GMP clinical packagers—for over encapsulation or overcoating

Compounding Specialized Dosage Forms for Investigational Use

How can our IDS blind a liquid formulation for a study?

- Flavored solutions
 - unpleasant odor and taste (NAC)
- Stability test (at RT and Refrig)

Issues Related to Dispensing Investigational Drugs

- Drug Supply Issues
- Dispensing drug from areas outside of the Investigational Drug Service
- Compounding specialized dosage forms for investigational use

Issues Related to Dispensing Investigational Drugs