Translational Research: Phase I Dose Escalation Studies

Jennifer L. Christensen, PharmD
Investigational Drug Clinical Pharmacist
Ben Taub General Hospital
Harris County Hospital District
Houston, TX

Jennifer_Christensen@hchd.tmc.edu

TGN1412

- March 13, 2006
- Phase I, single-center, double-blind, randomized, placebo-controlled, single escalating-dose
- 6 + 2
- Severe cytokine storm → multiorgan failure → ICU

Suntharalingam G, et al. NEJM 2006;355:1018-28.
Investigations into adverse incidence into clinical trials of TGN1412. London: MHRA, 2006. http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&useSecondary=true&ssDocName=CON2023822&ssTargetNodeId=389 (9/20/2007)

Objectives

- Define goals of dose-escalation studies.
- Describe the process for calculating Maximum Recommended Starting Dose (MRSD) in humans.
- Compare currently utilized Phase I methods for dose escalation in healthy volunteers.
- Determine the most appropriate cohort size for optimal outcomes in Phase I studies.

Phase I Dose-Escalation

- First-time-in-human or first-in-man
- Phase I – bridge from animal to humans
  - Safety and tolerability
  - Pharmacokinetics

Buoen, et al. J Clin Pharmacol 2005;45:1123-1136
Whitehead, et al. Biostatistics 2001;2:47-61

Phase I Dose-Escalation

- Current Issues
  - No consensus
  - Number of publications
  - Unknown animal and human comparability
  - Pharmacokinetic models

Winget M. [abstract] Control Clin Trials 1995;16(3 suppl 1):S40.
Buoen, et al. J Clin Pharmacol 2005;45:1123-36.
FDA CDER [homepage on the internet] http://www.fda.gov/cder/guidance/5541fnl.pdf (9/20/2007)

Estimating Maximum Starting Dose

- Determine No Observed Adverse Effect Level (NOAEL) mg/kg
  - Overt toxicity
  - Surrogate markers
  - Exaggerated pharmacodynamic effects

FDA CDER [homepage on the internet] http://www.fda.gov/cder/guidance/5541fnl.pdf (9/20/2007)

Estimating Maximum Starting Dose

- Human Equivalent Dose (HED)
  - Body surface area (BSA)
    - Common practice
    - More conservative
  - Body weight (mg/kg)
    - Alternate administration routes
    - Compartmental administration
    - Large proteins administered intravascularly

FDA CDER [homepage on the internet] http://www.fda.gov/cder/guidance/5541fnl.pdf (9/20/2007)

Estimating Maximum Starting Dose

Species	Reference Body Weight (kg)	Body Surface Area (m^2)	To Convert Dose in mg/kg to Dose in mg/m^2 Multiply by k_m
Human	60	1.62	37
Mouse	0.020	0.007	3
Rat	0.150	0.025	6
Dog	10	0.50	20
Monkeys	3	0.25	12
Micro-pig	20	0.74	27

Adapted from: FDA CDER [homepage on the internet] http://www.fda.gov/cder/guidance/5541fnl.pdf (9/20/2007)

Example: Patient 75 kg, 1.8 m^2
Rat dose is 25 mg/kg x 6 = 150 mg/m^2
150 mg/m^2 x 1.8 m^2 = 270 mg

FDA CDER [homepage on the internet] http://www.fda.gov/cder/guidance/5541fnl.pdf (9/20/2007)

Estimating Maximum Starting Dose

Species	To Convert Animal Dose in mg/kg to HED in mg/kg, Either:	
	Divide Animal Dose By	Multiply Animal Dose By
Human	--	--
Mouse	12.3	0.08
Rat	6.2	0.16
Dog	1.8	0.54
Monkeys	3.1	0.32
Micro-pig	1.4	0.73

Adapted from: FDA CDER [homepage on the internet] http://www.fda.gov/cder/guidance/5541fnl.pdf (9/20/2007)

Example: Patient 75 kg, 1.8 m^2
Rat dose is 25 mg/kg ÷ 6.2 = 4.03 mg/kg
4.03 mg/ kg x 75 kg = 302 mg

FDA CDER [homepage on the internet] http://www.fda.gov/cder/guidance/5541fnl.pdf (9/20/2007)

Estimating Maximum Starting Dose

- Species Selection
  - Absorption, distribution, metabolism, and excretion
  - Class experience
  - Human proteins / relevant receptors

FDA CDER [homepage on the internet] http://www.fda.gov/cder/guidance/5541fnl.pdf (9/20/2007)

Estimating Maximum Starting Dose

- Application of Safety Factor
  - For protection of human subjects receiving the initial dose
  - Default Safety Factor = 10
  - Allows for variability
    - Enhanced sensitivity
    - Toxicity detection
    - Receptor densities / affinities
    - Interspecies differences in ADME

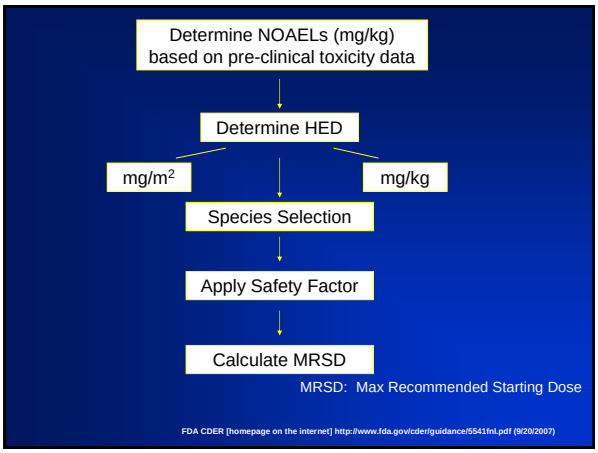
FDA CDER [homepage on the internet] http://www.fda.gov/cder/guidance/5541fnl.pdf (9/20/2007)

Estimating Maximum Starting Dose

Maximum Recommended Starting Dose (MRSD)
= HED / Safety Factor
= HED / 10

- Lower starting doses are often appropriate
- Pharmacologically active dose (PAD)

FDA CDER [homepage on the internet] http://www.fda.gov/cder/guidance/5541fnl.pdf (9/20/2007)



MRSD: Max Recommended Starting Dose

FDA CDER [homepage on the internet] http://www.fda.gov/cder/guidance/5541fnl.pdf (9/20/2007)

Dose-Escalation Studies

Survey of Phase I Dose-Escalation Trials Published 1995 – 2004

- 105 studies published in 5 major clinical pharmacology journals
- All major therapeutic areas were represented
- Most placebo-controlled (81.9%)
- 62.9% double-blind
- 2 – 19 dose levels

Buoen, et al. J Clin Pharmacol 2005;45:1123-36.

Dose-Escalation Studies

- Dose-Escalation Schemes
  - Linear – fixed dose increment (11%)
  - Logarithmic – relative dose increment is the same (21%)
  - Modified Fibonacci (0.3%)

Buoen, et al. J Clin Pharmacol 2005;45:1123-36.

Dose-Escalation Studies

- Dose-Escalation Schemes
  - Modified Fibonacci

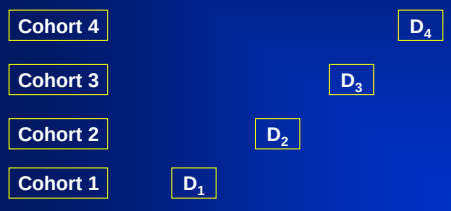
n = starting dose	% increase above preceding dose
2 n	100
3.3 n	67
5 n	50
7 n	40
12 n	33
16 n	33
Etc.	33

Buoen, et al. J Clin Pharmacol. 2005;45:1123-36.

Dose-Escalation Studies

5 major study designs

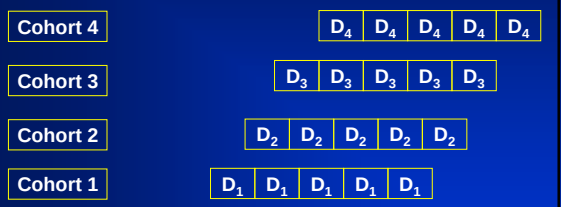
Parallel Group, Single - Dose



Buoen, et al. J Clin Pharmacol. 2005;45:1123-36.

Dose-Escalation Studies

Parallel Multiple - Dose



Buoen, et al. J Clin Pharmacol. 2005;45:1123-36.

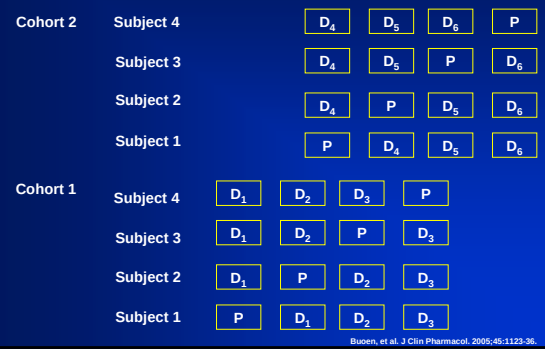
Dose-Escalation Studies

Parallel Single- and Multiple - Dose

Buoen, et al. J Clin Pharmacol. 2005;45:1123-36.

Dose-Escalation Studies

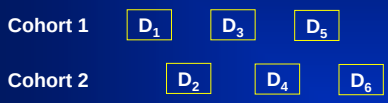
Grouped Crossover



Buoen, et al. J Clin Pharmacol. 2005;45:1123-36.

Dose-Escalation Studies

Alternating Crossover



Buoen, et al. J Clin Pharmacol. 2005;45:1123-36.

Dose-Escalation Studies

Crossover Design

- More patients = greater statistical power
- Intra-patient variability
- Persistence of drug effects
- Changes in underlying disease
- Dropout rates

Parallel Group

- No Carryover effects
- No intra-patient data

Dose-Escalation Studies

- Determining Cohort Size
  - Very low power
  - Relationship between detectable event rate and power is not linear
  - < 6 active subjects
  - As cohort ↑, probability of spontaneous events ↑
  - Cohorts > 10 subjects, little is gained

Therefore, active cohort size in Phase I dose escalation trials should be between 6 and 10 subjects

Buoen, et al. J Clin Pharmacol. 2003;43:470-6.

Dose-Escalation Studies

- Antibodies
  - Fewer assumptions
  - Removed from circulation by endocytosis (not metabolism)
  - Immediate and detectable effects on blood cells
  - Volume of distribution limited to the plasma volume
  - Uncertainties: differences between human and animal receptor sensitivity or density

FDA CDER [homepage on the internet] http://www.fda.gov/cder/guidance/5541fnl.pdf (9/20/2007)

TGN1412

- 6 + 2 study design
- Starting dose 0.1 mg/kg
- Pharmacologically active dose
- OKT3 as a comparator
- Primates 50 mg/kg
- 1 μg/kg

McLean AEM. Abstracts/Toxicology 2007;231:102.
Suntharalingam G, et al. NEJM. 2006;355:1018-28.
Investigations into adverse incidence into clinical trials of TGN1412. London: MHRA, 2006.
http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&useSecondary=true&ssDocName=CON2023822&ssTargetNodeId=389 (9/20/2007)

Conclusions

- Publication of all Phase I studies is ideal
- Calculation of the MRSD is a starting point
- Most Phase I studies utilize the parallel group single-dose design with a cohort size of 8 (6+2)
- Antibodies possess unique barriers to first-in-human dosing

Strategies for Expanding Investigational Drug Service Resources through Effective Communication and Negotiation

Robert Granko, PharmD, MBA
Assistant Director, Acute Care Services
Department of Pharmacy
UNC Health Care

ASHP Midyear Clinical Meeting
December 4, 2007

Disclosures

- Nothing to disclose relative to the contents of this presentation

Session Objectives

- Describe methods to optimize operational and financial results.
- Identify advantages and disadvantages of different extemporaneous compounding services to meet the needs of the investigators.
- Discuss future directions and opportunities in clinical research.

Objectives

- Provide specific strategies for expanding Investigational Drug Service resources.
- Describe methods for effective communication of Investigational Drug Service operational needs.
- Establish metrics to demonstrate Investigational Drug Service processes and performance to improve financial results.

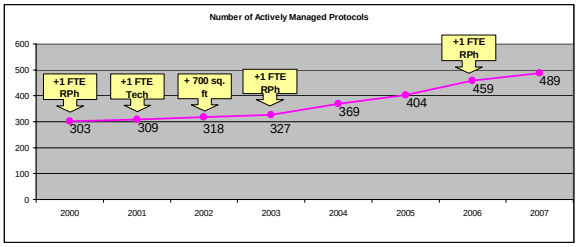
UNC Hospitals Investigational Drug Service

- Established Investigational Drug Service (IDS) satellite operations
  - 1981 - 1982
  - Staff: 0.5 FTE Pharmacist
- Study Volume
  - Managing: 12 studies
  - Revenue: none

Current Operations

- Space
  - Approximately 700 square feet (excludes office space)
- Staff
  - 5.75 FTE Pharmacists
  - 3.5 FTE Technicians
- Study Volume
  - Total number of managed protocols
    - 489

UNC Hospitals Investigational Drug Service



UNC HEALTH CARE

Arrival to IDS

- Assessment of the entire service
  - Scope of services
    - Operations
    - Relationships
- Plan for Service moving forward
  - Service metrics
  - Leader versus Manager
- IDS Advisory Board

UNC HEALTH CARE

IDS Advisory Board Overview

- IDS Advisory Board was implemented in 2000
- Goals of the Advisory Board:
  - Establish a comprehensive Investigational Drug Service
  - Help sustain the highest level of care for UNC research subjects
  - Meet regulatory requirements
  - Attract industry-sponsored research dollars
  - Provide IDS services in a cost-neutral environment

UNC HEALTH CARE

IDS Advisory Board Overview

- Chair
  - Director of the General Clinical Research Center
- Membership
  - Active investigators
  - Key therapeutic areas
- Aim
  - Maximize our effectiveness
  - Understand IDS operations

UNC HEALTH CARE

IDS Advisory Board

- Comparison with Peer Institutions
- Study Notebooks
- Acuity Worksheet
- Technological Enhancements
  - Scheduling software
  - Accounting software

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Peer Institutions

	UNC Hospitals	Hospital X*	Hospital Y^
Total Number of Managed Protocols Reported	404	390	400
Number of FTEs	7.75	11.4	11
Lead-in Protocol Time	6 weeks	4-6 weeks	4 weeks

*On average, takes 20hrs to write up protocol
*Goal is to re-coup 50% of personnel costs
^Waived 60k in 2005, for 2006 it will be zero (Departments will make decision to fund protocol)

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IDS Study Notebooks

- Featured select notebooks
  - Pediatrics and Psychiatry
- Receipt of protocol to opening of study
- Impact of strategy

Workload Measures

- Current measure
  - Productivity Management Data - Inpatient days
- Set out to create a worksheet
  - Categorically score the initial and maintenance resources needed to open a protocol
- Elements considered
  - Type of trial
  - Resources needed to write-up the protocol
  - Length of treatment and number of subjects
  - Types of drugs, how they are prepared, and packaged
  - Time investment

Acuity Worksheet

Number of Drugs Involved [including placebo(s)]: a. 1 point per drug	____
Type of drug: a. Oral or other ready-made form (i.e. inhalation, topical) (0 points) b. IV (5 point) c. Chemo/Compound (10 points)	____
Preparation of drug/product (i.e. heating, mixing, compounding): a. None (0 points) b. Less than 10 mins (1 point) c. 10-20 minutes (2 points) d. >20 minutes (3 points)	____
Placebo: a. None (0 points) b. Supplied by sponsor (1 point) c. Pharmacy to create (10 points)	____
Packaging of drug: a. Provided by supplier (0 points) b. Standard (5 point) c. Special (i.e. blister cards) (10 points)	____

- 20 protocol specific characteristics
- Protocol scoring
  - Assigned points and weighted heavily those activities that consumed the greatest amount of resources
- Complexity, overall acuity and resource consumption

Acuity Results

- Results:
  - 81% of the protocols were scored as Level 2 and 3
    - Level 1: No protocols identified
    - Level 2: GI, Hem/Onc, Medicine, Neurology, ID, and Ob/Gyn
    - Level 3: Pediatrics and Psychiatry
- Impact of strategy
  - Allow the IDS Advisory Board to set a fee structure with a goal of recovering a percentage of the total personnel costs
  - Allow the IDS to keep pace with the growing number of protocols through net FTE growth
  - Set groundwork for a fiscally responsible and sustainable Department

Technological Enhancements

- Scheduling software
  - Investigators understood expectations and how workload was scheduled
  - Helped the investigator appreciate actual study volume
  - Allowed to map individual pharmacist workload
  - Plan for vacations, sick time, occasional compassionate plea

Technological Enhancements

Technological Enhancements

- Accounting software
  - Invoice tool – database
  - Imported all data into software
    - Easy retrieval of information
    - Reproduce annual invoice
    - Level of reporting

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Clinical and Translational Science Award

- Clinical and Translational Science Award (CTSA)
  - CTSA program creates a definable academic home for the discipline of clinical and translational science at institutions
- Goals of the CTSA :
  - Encourage the development of new methods and approaches to clinical and translational research
  - Improve training and mentoring
  - Assemble interdisciplinary teams that cover the complete spectrum of medical research
  - Forge new partnerships with private and public health care organizations

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Clinical and Translational Science Award

- Position
  - Since 2000, IDS has:
    - 105% increase in the number of new protocols opened
    - 61% increase in the number of actively managed protocols
  - Actively managing approximately 500 protocols
  - Steady increase in turnaround time for studies to open

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Clinical and Translational Science Award

- Request and Return on Investment:
  - 1 FTE Clinical Inpatient Pharmacist
    - Decrease the study turnaround
    - Accommodate the increasing demand for IDS services
  - 1 FTE Accounting Specialist
    - Migration from the flat-fee structure to an acuity based, tiered billing structure that will bill Sponsors for actual work performed and as a result, capture additional revenue generated from large and complex studies

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Clinical and Translational Science Award

- Requested additional space of 1000 sq. ft
  - General preparation, dispensing, counseling and drug accountability tasks
- Requested additional space of 500 sq. ft
  - Support sponsor-led drug accountability visits (2-3 visits per day)
  - Suitable office location for pharmacists to prepare clinical trials for dispensation

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Summary

- Strategies for expanding IDS resources
  - Maximized effectiveness of Advisory Board
  - Increased awareness and understanding of IDS processes
  - Established workload measures and implemented technological enhancements
- Effective communication of IDS needs
  - Acuity worksheet
  - Used tools to demonstrate workload measures

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Questions?
UNC
HEALTH CARE

Investigational Drug Service

Management Aspects of Clinical Trials: Optimal Cost Analysis and Financial Justification

Janet Mighty
Assistant Director, IDS
The Johns Hopkins Hospital

IDS at Johns Hopkins Hospital

Investigational Drug Service

- Investigational Drug Service (IDS) satellite started in 1984 with 1 pharmacist
- Current Staff
  - 12 FTE pharmacists
  - 2 FTE pharmacy technicians
- Manage approximately 350 oncology protocols and 180 non-oncology

Purpose of IDS

Investigational Drug Service

MISSION Statement

- Patient care
- Education
- *Research*

IDS was developed to support clinical research

Objectives

Investigational Drug Service

1. Identify four aspects to consider in evaluating the financial performance of the IDS
2. Explain how revenue and expenses contribute to the IDS optimal fee structure
3. Discuss the "cost avoidance" strategy as an economic benefit to justify service

Scope of Services

Investigational Drug Service

- Dispensing, storage and record keeping
- Auditing studies
- IRB membership
- Coordinating satellite dispensing

Scope of Services

Investigational Drug Service

- Providing investigational drug information
- International study support
- Coordinating center

IDS Financial Performance

Investigational Drug Service

- Budget
- Performance Monitoring
- Billing and Reimbursement Monitoring
- Workload and Productivity

IDS Departmental Budget

Investigational Drug Service

- Revenue
- Operating Expenses

Revenue Sources

Investigational Drug Service

"Research dollars pay for research expenses"

- Current sources
  - IDS billing
  - Grants
  - Other
    - IRB, School of Medicine

IDS Operating Expense

Investigational Drug Service

Account Description	Amount
Salary Expense	
Benefits	
Drugs and Supplies	
Purchased Services	
Equipment repair/maintenance	
Grand TOTAL Operating Expense	

UHC IDS Survey 2007

Investigational Drug Service

- Required to cover cost via fees charged to the study

Response	Percentage
YES	55%
NO	45%

IDS Cost

Investigational Drug Service

	Total Cost	Personnel Cost	Operating Cost
Highest	$ 966,000	$ 966,000	$ 180,000
Mean	$ 320,335	$ 287,655	$ 39,394
Median	$ 182,500	$ 208,761	$ 13,000

(UHC Investigational Drug Service Survey 2007)

Salary Expense

Investigational Drug Service

- Tends to be the largest expense for IDS
- Includes benefits
- Ranges from $50,000 to $966,000 (UHC IDS survey)
- Depends on number of FTEs

Performance Monitoring

Investigational Drug Service

- Receive monthly reports
- Evaluate reports
- Explain variances

Actual vs Budget

Investigational Drug Service

Description	Actual	Budget	Variance
Pharm Serv Rev	1,200,000	1,420,000	220,000
Regular Salary	1,050,000	1,260,000	210,000
Drugs	120,000	130,000	10,000
M/S Supplies	4,000	6,000	2,000
Solutions IV	500	1030	530
Office Supplies	7,000	4,000	(3,000)
Other	18,500	18,970	470

Billing & Reimbursement

Investigational Drug Service

- Develop billing procedures
- Assure accuracy of billing
- Dedicate resources
- Collaborate with administration and financial representatives

Components of Bill

Investigational Drug Service

- Administrative fee, initiation fee
- Dispensing
  - Oral, IV, chemotherapy, gene therapy
- Drug and supply costs
- Randomization
- Storage
- Monitoring visits/close-out

Components of Bill

Investigational Drug Service

- Compounding/blinding of drug
- Controlled substance handling
- FDA audit
- Product destruction
- Shipping labor cost
- Courier service
- Other

Budget / Billing Template

DESCRIPTION OF SERVICE	YEAR 1 ($)	YEAR 2 ($)
ADMINISTRATIVE SETUP		N/A
INVENTORY MANAGEMENT	$ -	$ -
DISPENSING COSTS	$ -	$ -
DRUGS	$ -	$ -
COMPOUNDING PHARMACY SERVICES	$ -	$ -
PREPARATION OF RANDOMIZATION	$ -	N/A
MISCELLANEOUS / OTHER	$ -	$ -
TOTAL	$ -	$ -
	plus additional patient charges	*plus additional per patient charges*

Administrative Set-up

Investigational Drug Service

- Fee for the various activities required to implement a protocol
- Usually a one time fee
- Set fee for all studies
- Variable based on estimated hours

Inventory Management

Investigational Drug Service

- Fee for study drug storage and inventory control
- Consider various storage locations (i.e., refrigerator, freezer, room temperature)
- Receipt and return of drug
- Physical inventory counts

Dispensing Costs

Investigational Drug Service

- Actual cost for the preparation of the study drug
- Includes pharmacist and technician labor
- Hourly rate +/- benefits
- Oral preparation, IV preparation, chemotherapy, gene therapy

Drug & Supply Cost

Investigational Drug Service

- Charge for drugs and/or supplies obtained through the pharmacy
- Actual cost + markup

Compounding

Investigational Drug Service

- Sterile or oral bulk compounding
- Blinding of study medication
- Placebo preparation

Other

Investigational Drug Service

- Randomization
- Shipping
- Courier cost
- Supply cost
- Language translation

Aspects to Consider

Investigational Drug Service

- Optimal fee structure
- Accuracy and timing of investigator budget estimate
- Communication with financial representatives
- Information systems
- Method of collection

Workload & Productivity

Investigational Drug Service

- Justify resource allocation
- Determine workload units
  - Doses dispensed (inpatient)
  - Outpatient prescriptions filled
  - Budgets prepared
  - Dispensing procedures completed
  - Study close-outs

Workflow Analysis

Activity	IDS Central (hours/month)	IDS Pediatrics (hours/month)	IDS Oncology (hours/month)
Protocol Review/ Development	335	84.5	242
Protocol Implementation	357	46.25	242.5
Inventory Management	81.6	5.6	201.8
Meetings	52	14.5	49
Quality Assurance	16	combined w/Central	5
Drug Information	5	7.5	10
Finances	62	5	26
International Support	140	0	16
Auditing	64	0	1
IRB Support	103	0	24
Administrative	8	14	14
Total	1223.6	177.35	831.3
FTEs (including 14% neg time)	8.05	1.17	5.47

Justification of Services

Investigational Drug Service

Does cost avoidance justify the cost of the Investigational Drug Service?

Definition

Investigational Drug Service

- A technique to demonstrate the benefits of some action by comparing the money saved by taking the action against money that would be spent by not taking the action.

Cost Avoidance

Investigational Drug Service

Economic benefits of investigational drug services at an academic institution *Am J Health-Syst Pharm*. 2004;61:27-32. LaFleur J, Tyler LS, Sharma RR.

Cost Avoidance

Investigational Drug Service

- Methods
  - Review of study protocols and dispensing data
  - Identified
    - Studies of marketed drugs that were being evaluated for new indications
    - Studies of non-FDA-approved drugs for which a marketed alternative exists

Cost Avoidance

Investigational Drug Service

- Methods cont.
  - Collect data
  - Tabulate costs for all active and placebo doses
  - Determine an alternative for investigational drugs

Cost Avoidance

Investigational Drug Service

- Results
  - Total drug cost avoidance for 107 studies over 2 fiscal years totaled $5,088,668
  - Total revenue generated ($211,760) represents 4% of total drug cost avoidance + revenue ($5,300,428)

Cost Avoidance

Investigational Drug Service

Conclusion:

An IDS accounted for substantial drug cost avoidance over two fiscal years

Regulatory Requirements

Investigational Drug Service

- FDA www.fda.gov
- Billing Compliance

Charging for an IND

Investigational Drug Service

"Charging for an investigational drug in a clinical trial under an IND application is NOT permitted without the prior written approval of FDA"

(21 CFR 312.7 Promotion and charging for investigational drugs.)

Contact Information

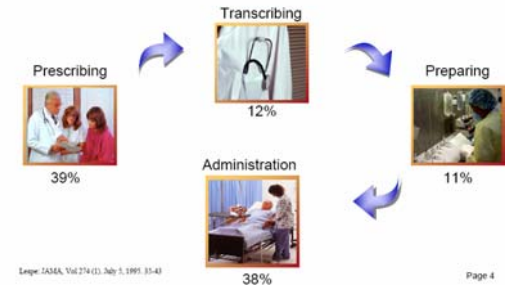
Investigational Drug Service

Janet Mighty
The Johns Hopkins Hospital
Department of Pharmacy Services
600 North Wolfe Street
Baltimore, Maryland 21287-6180
410.955.6337 (phone)
410.614.8074 (fax)
JMIGHTY@JHMI.EDU

Quality Control in an Investigational Drug Pharmacy

John Petrich, RPh, MS
Cleveland Clinic
petricj@ccf.org

Medication Use System - Error Occurrence



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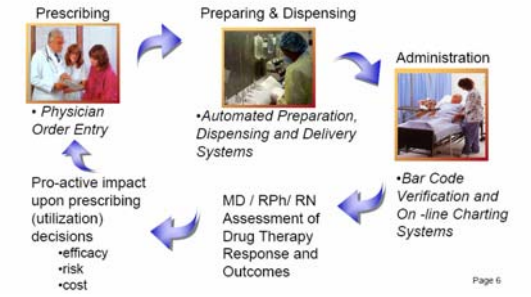
Key Strategies for Medication Use System Redesign



Integration

- Systems aligning with pharmacy department operations
  - Automation
  - Information
  - Accessibility

4

Bar code technology in hospital pharmacy cuts errors

Reduces dispensing mistakes, potential adverse events

Poon EG, Cina JL, Churchill W et al. Medication dispensing errors and potential adverse events before and after implementing bar code technology in the pharmacy. Ann Intern Med. 2006; 145(6):426-34.

6

Poon, et al

- Before and after study using direct observations
- Hospital pharmacy at a 735 bed tertiary care academic medical center

7

Poon

- Objective – to evaluate whether implementation of bar code technology reduced dispensing errors

8

Poon

- Intervention
  - Bar code assisted dispensing system in 3 configurations
    - 2 configurations – all doses scanned during the dispensing process
    - 1 configuration – only one dose scanned if several doses of the same medication dispensed

9

Poon

- Measurements
  - Target dispensing errors
  - Target potential ADEs

10

Poon

- Results
  - Before bar coding, 0.19% of dispensed doses had errors with the potential to harm patients
  - After bar coding, the rate of potential ADEs from dispensing errors decreased to 0.07%

11

Poon

- Results
  - Configurations requiring all doses scanned
    - 93% to 96% relative reduction in target dispensing errors ($p<0.001$), 86% to 97% relative reduction in potential ADEs ($p<0.001$)
  - Configuration not requiring all doses scanned
    - 60% relative reduction in target dispensing errors ($p<0.001$), increased incidence (2.4 fold) of potential ADEs ($p=0.014$)
    - Potential life threatening ADEs

12

Poon

- Limitations
  - The authors used surrogate outcomes
  - Assessors not masked to the purpose of the study
  - Controlled substance fill process excluded

13

Bar code technology
– Cost benefit analysis

14

The “cost of quality” isn’t the price of creating a quality product or service. It’s the cost of NOT creating a quality product or service.

American Society of Quality

15

In short, any cost that would not have been expended if quality were perfect contributes to the cost of quality.

16

Implementation of a bar code assisted medication dispensing system in hospital pharmacies can result in a positive financial return on investment for the health care organization

Maviglia SM, Yoo JY, Franz C et al. Cost-Benefit Analysis of a Hospital Pharmacy Bar Code Solution. Arch Intern Med. 2007;167:788-794.

17

Maviglia, et al

- Primary outcome
  - Net financial cost and benefit during the initial 5 year period
- Secondary outcome
  - Time when total benefits equaled total costs

18

Maviglia

- Overview
  - Tertiary care academic medical center
  - Bar codes affixed to all medications at the unit dose level

19

Maviglia

- Costs
  - Software/hardware
  - Infrastructure
  - Planning
  - Training
  - Repackaging
  - Lease agreements
  - Maintenance
- Benefits
  - Savings associated with ADE prevention

20

Maviglia

- Data collection – costs
  - Accounting records, meeting minutes, project management system, observation
  - Hours converted into dollars based on wages

21

Maviglia

- Data collection – benefits
  - Calculated directly from observed rates of potential dispensing errors both before and after the intervention
  - Potential ADEs were defined as dispensing errors with the potential to harm patients

22

Maviglia

- Statistical analysis
  - Aggregated by fiscal quarter and adjusted for a constant interest rate, value of money, and inflation
  - Cost of ADE estimated from the literature

23

Maviglia

- Assumptions
  - 34% of the potential ADEs would be intercepted
  - 13.4% of the remainder result in actual ADEs

Leape LL, Bates DW, Cullen DJ et al. ADE Prevention Group. Systems analysis of adverse drug events. JAMA, 1995;274:35-43.

Bates DW, Boyle DL, Vander Vliet MB et al. Relationship between medication errors and adverse drug events. J Gen Intern Med. 1995;10:199-205.

24

Maviglia

- Results
  - Total cost = $2.24 million in inflation, time value adjusted 2005 dollars
  - Cumulative benefit = $5.73 million
  - The break even point for the hospital investment occurred within 1 year after becoming fully operational

25

Maviglia

- Strengths
  - Prospective data
  - Published estimates rather than expert opinion used
- Limitations
  - Single center
  - Pre-post comparison of error rates

26

Maviglia

- Comment
  - The two most important determinants of benefit
    - Proportion of dispensing errors that result in ADEs
    - Cost
  - The analysis appeared to be robust when these variables were varied widely

27

28

Web based system

- Automation adds
  - Safety and accuracy
  - Consistency
  - Efficiency

29

Web based system

- Reduces paperwork and handwriting
- Brings the Investigational Drug Service in line with other pharmacy operations in terms of data management

30

Web based system

- Supports technician preparation with pharmacist verification
- Dispensing is limited to arms that the subject is enrolled
- Initial prescription and refills
- Custom labels with high degree of flexibility

31

Web based system

- Financial management
  - Set up and manage accounts
  - Protocol setup, inventory, randomization and dispensing fees automatically collected
  - Ad hoc fees (shipping, capsule preparation) can easily be billed to an account
  - Ability to track cost avoidance
  - Automatically generate invoices and statements of activity

32

Web based system

- Financial management (cont)
  - Accounts receivable
    - Ability to record payments within system
    - Numerous reports
      - Aging reports
      - Payment reports
  - Extract can be generated and sent to your hospital billing system
  - Automation of billing is big time saver

33

Web based system

- Reports
  - Several built-in reports
    - Workload
    - Financial metrics
    - Protocol reports
      - Master Log
      - Billing Summary
      - Drugs Needing to be Reordered
      - Expired or Soon-to-Expire IRBs
      - Patient Returns

34

Web based system

- Safety and accuracy
  - Barcodes allow quick scanning and correct identification
  - Pharmacist verification of technician work
  - Patient must be enrolled in an arm in order to dispense
  - Warnings for expired drugs and IRB expirations
  - Adaptable labels

35

Why move off paper to an automated Web based system?

- Reduce errors and rework
  - Barcodes, safety design, safe labels
- Improve efficiency
  - Dispensing, billing, reports greatly simplified with Web based system
  - Reduces dispensing effort and allows more clinical activity or increased protocols
  - Scales with increased IDS activity – paper doesn't

36

Web based system - benefits

- Improved Efficiency
  - Ability to manage a higher volume of studies
  - Reduced non-value added work (billing, manual inventory records)
- Improved Safety and Accuracy
- Electronic Records
- Potential Billing Capture Improvement
  - Reduced write-offs through better management
  - Reduced missed charges

37

Web based benefits

- Access!

38

Pre-printed physician order forms

- **How can potential medication errors be minimized when dispensing investigational drugs to better ensure patient safety and improve adherence to the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) medication management standard?**

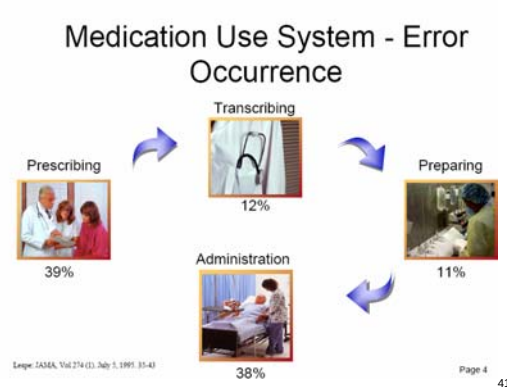
Tamer H, Shehab, N. Am J Health-Syst Pharm. 2006;63(11):1022-8.

39

Pre-printed physician order forms

- The Institute of Medicine has estimated that 44,000-98,000 deaths may be caused annually by medical errors in hospitals.[1]
- Many of these errors occur during the ordering, transcribing, dispensing, and administering of medications.
- The Food and Drug Administration reports that medication errors lead to at least one fatality each day and injure up to 1.3 million individuals yearly.[2]
- Among the most frequently reported medication errors are those that occur during medication ordering and transcribing. These errors are caused by such factors as illegible handwriting, misuse of common abbreviations, and confusion between look-alike or sound-alike drugs.[3,4]

40



41

Pre-printed physician order forms

- JCAHO requires that hospitals address the procedures for ordering drugs and transcribing drug orders when developing and implementing a safe medication management system; this requirement must also be met for investigational drugs.[5]
- Specifically, JCAHO requires that medication orders be clearly written and transcribed accurately in order to reduce the potential for error or misinterpretation when orders are written or orally communicated.[5]

42

Pre-printed physician order forms

- Safeguards
  - Documents informed consent in pharmacy records
  - PI or sub-investigator signature
  - Eliminates transcription errors
  - Provides a back-up for dispensing and drug accountability records
  - Billing compliance

43

Billing compliance

- Drugs provided as part of a study included on the pre-printed physician's order form
- Differentiates billable from non-billable drugs

44

Research Pharmacy

- Not all research drugs are stored and dispensed by the pharmacy
- Well defined criteria dictate whether the pharmacy or the investigator control the study drug in some academic medical centers

45

Criteria

- Pharmacy control of study drug
  - inpatient studies
  - sterile preparation, sterile technique
  - blinding
  - repackaging, labeling
  - space
  - time and resources
- Investigator control with remote, periodic pharmacy monitoring
  - outpatient studies
  - oral drug packaged and labeled for dispensing
  - convenience factor
  - no need for the resources listed in pharmacy criteria

46

Power

47

When the lights go out, will you know what to do?

48

What does the Joint Commission require?

49

How can pharmacy approach the issue of investigator controlled drugs at a large academic medical center?

Remote, periodic, quality monitoring

50

It's been said that if you don't measure something, you can't improve it.

51

Quality Measurement

- Requires a tool

52

Data Collection and Analysis Tools

A check sheet is a structured, prepared form for collecting and analyzing data.

A generic tool that can be adapted for a wide variety of purposes.

When to Use a Check Sheet

1. When data can be observed and collected repeatedly by the same person or at the same location.
2. When collecting data on the frequency or patterns of events, problems, defects, defect location, defect causes, etc.
3. When collecting data from a production process.

American Society for Quality

53

It's even more important to realize that your choice of metrics bounds your organization's future. If there is a key success factor and it's not acknowledged or tracked, it may as well not exist.

American Society for Quality

54

The Quality Monitoring Checklist measures compliance with JCAHO standards

Investigator compliance is assessed quarterly

Monitoring checklist

- Elements of the checklist are derived from JCAHO standards

Joint Commission
on Accreditation of Healthcare Organizations
Setting the Standard for Quality in Health Care

The Cleveland Clinic Foundation
Department of Pharmacy
Investigational Drug Inspection

Location:_____Study Title_____Date_____

Investigational Medication Storage	YES	NO	N/A
1. Medication storage area is clean and well organized.	____	____	____
2. Investigational Medications storage area secured with limited access.	____	____	____
3. Investigational Medications requiring special conditions (i.e., room temp., refrigeration, protected from light, ect. properly stored	____	____	____
4. Investigational medications are properly labeled for investigational use and are separate from other non-investigational drugs.	____	____	____
5. Investigational medications are in date.	____	____	____
6. Returns and expired investigational medications identified and separate from active inventory.	____	____	____
Investigational Medication Refrigerators			
1. Refrigerator is stored in a secure area with limited access.	____	____	____
2. Refrigerator is clean and does not contain excessive frost.	____	____	____
3. Operating at proper temperature (36-46° F ; 2-8° C).	____	____	____
4. A Temperature log is being kept.	____	____	____
5. Investigational medications under refrigeration are properly labeled and separate from non-investigational drugs.	____	____	____
6. Refrigerator does not contain food or other non-drug items.	____	____	____
7. Investigational medications are in date.	____	____	____
8. Returns kept under refrigeration are identified and stored separate.	____	____	____
Investigational Records			
1. A current copy of protocol available and kept in a secure area.	____	____	____
2. A current IRB letter of approval is on file.	____	____	____
3. IRB Number_____.			
4. The IRB annual progress report for renewal or final report of completion is due on or before _____(date).			
5. Names of investigator, coordinator and sponsor are available:	____	____	____
Principal Investigator:_____Study coordinator:_____			
6. Pertinent information on study medication available for patient.	____	____	____
7. Consent forms are being obtained on every subject prior to enrolling the subject into the study and are kept in a secure area.	____	____	____
8. Documentation is being completed/signed by authorized personnel	____	____	____
9. Records of shipment from suppliers are kept.	____	____	____
10. Dispensing log is being kept and coincides with the current inventory	____	____	____
11. Destruction is being done per FDA regulations and per sponsors wishes	____	____	____

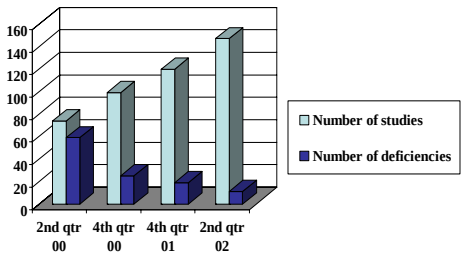
Monitoring program

- Deficiencies are flagged, and remedied in a timely manner
- Investigator is notified of deficiency

Monitoring program

- Retrospectively track deficiencies over time to assess the impact of the program
- Most dramatic impact seen at the outset, but persists a year later and beyond

Impact of remote surveillance



Conclusions

- Monitoring of remote drug storage, dispensing, and record keeping enhances the quality of health services
- Investigator awareness of the JCAHO standards improved over time in association with pharmacy intervention

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References

1. Kohn KT, Corrigan JM, Donaldson MS, eds. To err is human: building a safer health system. Washington, DC: National Academy Press; 1999.
2. Food and Drug Administration. Medication errors. www.fda.gov/cder/handbook/mederror.htm (accessed 2007 July 30).
3. National Coordinating Council for Medication Error Reporting and Prevention. About medication errors. www.nccmerp.org/aboutMedErrors.html (accessed 2006 Dec 29).
4. Institute for Safe Medication Practices. ISMP's list of error-prone abbreviations, symbols, and dose designations. www.ismp.org/Tools/abbreviationslist.pdf (accessed 2007 July 30).
5. Section 1: medication management. In: Comprehensive accreditation manual for hospitals: the official handbook. Oak-brook Terrace, IL: Joint Commission on Accreditation of Healthcare Organizations; 2004:MM1-20.

62

Extemporaneous Pharmaceutical Compounding For Clinical Research

Joanne Whitney, Pharm.D., Ph.D.

"And thou shalt make it an oil of holy ointment after the art of the apothecary"
Exodus 20:25

Renaissance of Compounding

- Special Venues
- Limited Dosages and Dosage Forms
- Drug Shortages and Discontinuations
- Public Demand for Natural Products
- Heavy Marketing/Big Cash Profits
- Clinical Trials

COMPOUNDING

- Preparation of Dosage Forms
- Requires a Pharmacy License
- Requires a Prescription or Drug Order
- Some Anticipatory Compounding Allowed
- Beyond Use Date

MANUFACTURING

- Production, Preparation, Processing of Drugs
- Repackaging for Resale
- Requires Registration with FDA
- Expiration Dating

Good Manufacturing versus Good Compounding Practices

Types of Compounded Products

Powders – Charts, Dentrifrices, Effervescents
Tablets
Capsules – Hard Gelatin or Soft
Lozenges/Troches/Pastilles/Lollipops
Suspensions, Solutions
Suppositories
Gels
Pluronic Gels
Pastes
Creams
Ointments
IV, Epidural, Intrathecal Sterile Solutions

COMPOUNDING INFLUENCES

Commercial Interests
Consultants
Compounding Supply Companies
Compounding Pharmacies

Where is Health-system Pharmacy?
Where is Academia?

COMPOUNDING PHARMACIES

- Bio-identical Hormone Replacement
- Pain Control including IT
- Ophthalmic Preparations
- Cosmeceuticals, Dermatology
- Pediatric, Geriatric, Veterinary
- Autism
- Herbal and High Dose Vitamins
- Homeopathic Cures
- Cash Consulting

Attempts to Curtail Pharmacy Compounding

FDA Modernization Act Unconstitutional

CHASM – 2005

Midland, Texas Suit

Pharmaceutical Manufacturers

Questionable Compounding Practices

Compounding Pharmacy Deaths\Injuries

Questionable Compounding Practices

- No Sterility or Pyrogen Testing
- No Content Testing
- From 1990 to 2003, FDA claimed 3,000 substandard prescriptions:
  - Lower concentration than stated
  - Bacterial, fungal contamination
  - Calculation errors
  - Incompatibilities
  - Stability Problems
  - No Absorption, No Bioavailability

Compounding Pharmacy Deaths/Injuries

- S. C. – Steroid Fungal Contamination – 1 death
- Mo. – Chemo Adulteration - ??
- Texas – Clonidine Suspension - 1 death
- N. C., Ariz.–Lidocaine Gel – 2 deaths
- Walnut Creek – IT betamethasone
  Serratia – 40 hospitalized – 3 deaths
- Nebraska – Cardioplegia – 4 deaths

Who Regulates Compounding?

States' Board of Pharmacy

DEA

Joint Commission

NIOSH

FDA

US Pharmacopeia

Granting Agencies

USP 795 Non-Sterile Compounding

P&Ps, Formulation & Compounding Records, Quality Assurance, Beyond Use Dating, Pertinent Chapters

USP 797 Sterile Compounding

Risk Levels

Low – Simple Manipulations
Medium – Multiple Manipulations
High – Non Sterile Powders/Equip

Hoods – ISO 5-all levels; Clean Room – ISO 7- high
Barrier Isolators – ISO 5

Record Keeping/Quality Assurance

- Standard Operating Policies &Procedures
- Equipment Maintenance Records
- Environmental Quality Checks
- End Product Testing
- Stability Records
- Analytical Test Results, where necessary
- Written and Practical Tests of Employee Competence & Education

Formulation & Compounding Records

- Name, Strength and Dosage Form
- Ingredients, Source, Quantity, Lot, Expiration, USP Standard
- Equipment Needed
- Mixing Instructions, Calculations
- Author or Source of Recipe
- Beyond Use Date
- Container and Label Used
- Amount Prepared
- Date of Preparation
- Signature of Preparer and Pharmacist
- Assigned Internal Lot or Identification Number

RESEARCH COMPOUNDING BUSINESS MODELS

FOR PROFIT

Independent Retail Pharmacy

Retail Pharmacy Owned by Hospital/School

NON-PROFIT

Academic Unit of School - Licensed

Independent Part of the Hospital Pharmacy

Part of Investigative Drug Service

PERSONNEL

Director – Chemical, Clinical, Financial Administrative, Marketing

Pharmacists

Technicians

Marketing/Financial Person

Students

Lab Helpers

How is Business Generated?

Traditional Marketing Techniques

Recommendations by Colleagues/Users

Co-Investigators on Grants

Co-Authors on Research Papers

Presentations at Major Meetings

Consulting with Regulatory Agencies

Repeat Business

TYPICAL E-MAIL REQUEST

I got your contact information from XXXXX from whom I am planning to purchase c13 enriched acetate.

She said that you might be able to help me figure out the cost of making the required dosage from the labeled salt For infusion into humans for my study. Since this is for infusion Into humans could you please let me know the procedures of sterility, Storage and expiration? Also, what would be the turnaround time to make the dosage?

The proposed study is to be conducted in the MRI imaging lab at the XXXX campus. Please let me know.

Setting Up Research Compounding

Clarification with PI

Formulation Study

Production of a Quotation - Can be Composed for Grant Application

Scheduling

Creation of Formulation Records

Production and Quality Assurance

Follow-up

PRODUCING A QUOTATION

Calculate Number of Drug Units

Consider Stability

Determine Packaging

Cost of Goods, Labor & Overhead

Special Procedures – Sterility, Pyrogen, Content Testing, Randomization, etc.

Set a Response Date – typically 6 weeks

PRICING for BASIC COMPOUNDING

Cost of Goods –2-5% Markup

+

Labor - Pharmacists' Time/Hour

Technicians' Time/Hour

Salary plus Benefits

+

Overhead – Pharmacists' & Techs' Time X Calculated Amount

PRICING FOR OTHER SERVICES

Consultation - Hourly

Blinding, Randomization & Keeping the Blind– Fixed Rate

Sterility & Pyrogen Testing – Fixed Rate

Content Analysis – Published Analysis – HPLC- Fixed Rate

Content Analysis – New Compound – C of G + Labor & Overhead

Stability Studies – C of G + Labor & Overhead

BRIEF HISTORY OF DPSL

- Founded 1937 – Pharm. Technology
- 1960-70's – FDA Registered
- 1983-1990 – Home Infusion
- 1990 – 2003 - TPN, IV Piggybacks, CRRT, Other Products for Hospital
- 2001 - Clinical Trials, Innovative Dosage Forms, Scholarship, Teaching

DPSL Recurrent Products

- Drug Dosage Forms for Hospital
- Coal Tar Ointments for Psoriasis
- Cardioplegic Solutions for Surgery
- Intrathecal Syringes for Pain Clinic
- Sterile Glycerol /Pumps/Nerve Sclerosis
- Rx for Human and Animal Patients
- California Donor Transplant Network
- Teaching, Consulting, Expert Witness

CLINICAL TRIAL INVOLVEMENT

- Researching Methodology, Logistics, Transportation, Cost of Studies
- Providing Detailed Quote and Plan
- Blinding, Block Randomization
- Managing Single & Multicenter Trials
- Compounding/Packaging Dosage Forms
- Process Validation, Beyond Use Dating
- Sterility, Pyrogen, Content Testing

Capsules – Active vs. Placebo

Powder, Triturated Tablets Mixed with Excipients and Machine Filled or Hand Punched or Encapsulated Whole Tabs

- Bupropion, nortriptyline, fluoxetine
- Ginko, Cinnamon, Saw Palmetto
- Calcium 41 at Lawrence Livermore
- Compliance Aids

About 100 Capsule Studies/Year

Other Research Dosage Forms

- Suppositories – Indomethacin, Papaverine
- Ointments/Gels – Ferrets, New Drugs
- Mouthwash – Sucralfate, GMCSF
- Powders – Citrucel vs. Placebo
- Nasal Sprays – Naloxone/Nalbuphine
  Cystic Fibrosis Testing
- Suspensions -Augmentin – Dog bite

PARENTERAL STERILE STUDIES

Stable Isotope Preparations

- ^{2}H & ^{13}C Acetate, Leucine, Glucose, Palmitate, Glycerol, Lactate, Bicarbonate
- $^{42,46}Ca$, $^{68,70}Zn$, ^{54}Fe
- ^{13}C Cholic Acid
- ^{2}H Nicotine, Cotinine

Other Interesting Preparations

- R-parathyroid hormone, teriparatide(Forteo®)
- Sterile India Ink

CURIOSITY CABINET

- Chicken Soup vs. Spinach Soup
- Humidity Control for MJ Cigarettes
- Prolotherapy – Dextrose, Phenol
- GE MRI – 13C Magnetized Solution
- Grifols Sterile Dose Compounder
- Sex Toys - Viricides

TEACHING

- Advanced Practice Experience
  6 Weeks - Project & Talk
- Certification in Chemotherapy
- Pharmacy Interns
- Hank Libby Scholarship for Formulation Research
- Residency?

REVENUE USES

Increase Staff as Business Increases

Provide More Educational Opportunities For Employees

Diversify Services

Purchase New Equipment/References

Renovate Working Areas