Study Drug Formulation and Supply Issues

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Clinical Trial Drug Supply Logistics Topics

- Single Center vs. Multi-Center Trials
- Sourcing of Study Drug
- Blinded vs. Open-Label
- Primary and Secondary Packaging
- Labeling
- Impact of Treatment & Enrollment Durations
- Subject Specific vs. IVRS/IWRS
- Storage Condition Considerations
- Distribution Logistics
- Disposition of Study Drug at Conclusion of Study

Clinical Trial Drug Supply
Single Center vs. Multi-Center

Practice of Pharmacy

(prescription)

vs.

“cGMP” Processing

(batch record)

Clinical Trial Drug Supply
Overview of cGMP Requirements

- GMP = Good Manufacturing Practices
- “c” = current
- Federal Regulations (FDA) required when introducing clinical trial materials into interstate commerce.
- cGMP’s are quality standards covering all aspects of pharmaceutical processing and distribution
- GMP philosophy requires that activities are documented by two individuals as “Done By” and “Checked By”

- Pharmacy – Regulated by State Boards of Pharmacy

Definitions

- Drug Substance: Active Pharmaceutical Ingredient (API) or “Raw Drug Substance”
- Drug Product: a finished dosage form, for example, tablet, capsule, solution, etc., that contains an active drug ingredient generally, but not necessarily, in association with inactive ingredients. The term also includes a finished dosage form that does not contain an active ingredient but is intended to be used as a placebo.

Clinical Trial Drug Supply
Sourcing of Study Drug

- API (Active Pharmaceutical Ingredient) or raw material
- Bulk Drug Product - Finished dosage form (e.g. tablet, capsule, solution).
- Packaged Drug Product – Bottles, blister cards, etc.
- Vendor Selection
  - Utilize GMP compliant contract manufacturing organizations (CMO).
  - Assure robust supply chain with dependable lead times.
- Non-Drug Products
  - Packaging Components (bottles, kit boxes, labels, etc.)
  - Study accessories (test kits, totes, counting trays etc.)

Lead Time for the Entire Supply Chain (Months!!)

- Time to receive API and all required excipients
- Time to receive components: bottles, caps, cotton, boxes, labels, seals etc.
- Time for Manufacturing (including getting in the manufacturing queue)
- Time for Primary packaging and any resting period
- Time for Secondary packaging and labeling
- Time for Distribution to sites

In all of above also factor in:

- Time for transit between vendors
- Time for custom clearance

Quantities to Order

- (Dosage strength X doses/day) X (# dosing days/subject + plus side of each visit window) X total number of subjects

PLUS

- Overage: to account for manufacturing waste, loss, damage, AND extra supplies at the sites that may never be used.
  - Industry standard is 15-30% for a traditional trial based on study size (e.g. most phase III studies use 30%)
  - Overage can be decreased via use of an IVRS/IWRS
- Must be based on the final bottle, kit etc. configuration as the configuration itself may already have overage

Forecasting for Resupplies

Factor in:

- Expiry/Retest dates
- Lead time/costs to manufacture multiple batches
- Storage constraints at vendor packaging materials
- Transportation/Customs costs for multiple shipments
- Develop programs/reports during the planning phase that will take enrollment rates, premature withdrawals, dose suspensions, etc. into account

Clinical Trial Drug Supply
Blinded vs. Open-Label

- **Common Blinding Methods**
  - Over encapsulate active tablets/capsules and manufacture matching placebo capsules
  - Identically formulated active and placebo dosage forms

- **Blindness Evaluation Includes**
  - Drug Product
  - Packaging
  - Labeling

Clinical Trial Drug Supply
Blinding

- Appearance (Color)
  - Try to avoid dyes related to sensitivities (e.g. yellow – tartrazine)
- Taste – More common with liquid formulations.
- Smell
- Texture – More of an issue with non-solid oral dosage forms.

Sample Kit Label

Protocol Number: INO-PD-P2-2008
Study Acronym: SURE-PD

Enrollment ID No.: XXXXX Kit Box No.: X

Subject Number: _____ Subject's Initials: _____

Date Dispensed: _____

Contents: 6 bottles, each containing 100 capsules of Inosine 500 mg or matching Placebo

Directions: Use only as directed by a physician. To be taken by mouth. This product is an investigational product to be dispensed only by a qualified investigator.

Storage: Controlled Room Temperature 15° - 30°C (59° - 86°F)

Caution: New drug limited by law to investigational (clinical trial) use only. **Keep out of reach of children.**

Manufactured by: Azopharma Contract Pharmaceutical Services, 10320 USA Today Way, Miramar, FL 33025

Distributed by: Clinical Materials Services Unit (CMSU), 77 Ridgeland Rd., Rochester, NY 14623

Sample Bottle Label

Protocol No.: INO-PD-P2-2008 **Study Acronym: SURE-PD**

Enrollment ID No.: XXXXX Kit Box No.: X

Bottle No.: X Date Dispensed: _____

Subject No.: _____ Subject's Initials: _____

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Clinical Trial Drug Supply
Blinded vs. Open-Label

Blinded Dosing Regimen

Example:

- Three Treatment Arms (Placebo, 100 mg and 300 mg)

  Take One (1) capsule from each of three bottles once daily.

  - Placebo = Three bottles of placebo capsules (P – P – P)
  - 100 mg = One bottle of 100 mg capsules and two bottles of placebo capsules (A – P – P)
  - 300 mg = Three bottles of 100 mg capsules (A – A – A)

Clinical Trial Drug Supply
Blinded Titration Phase

Example:

- Two-week dose titration period (150 mg up to 300 mg)
- Week 1 – Subjects will take one capsule daily from Bottle A.
- Week 2 – Subjects participants will continue to take one capsule daily from Bottle A and add one capsule daily from Bottle B.

Treatment Arm	Bottle A	Bottle B
150mg	150mg Capsules	Placebo Capsules
300mg	150mg Capsules	150mg Capsules
Placebo	Matching Placebo Capsules	Matching Placebo Capsules

Clinical Trial Drug Supply
Blinded Dose Reduction

Example:

- Step 1 – Discontinue capsule from Bottle A

Treatment Arm	Bottle A	Bottle B
150mg	150mg Capsules	Placebo Capsules
300mg	150mg Capsules	150mg Capsules
Placebo	Matching Placebo Capsules	Matching Placebo Capsules

Clinical Trial Drug Supply Subject Use Considerations

- Formulation affects compliance:
  - Large tablets/capsules may be difficult to swallow
- Packaging affects compliance:
  - Child resistant bottles caps and blister packets may be a problem to open
  - Small, poorly differentiated labels may cause confusion

Clinical Trial Drug Supply
Primary Packaging

Refers to packaging that immediately encloses a product.

It provides most of the strength and barrier needed to safeguard a product product's purity, potency and integrity from the time it is packaged until it used by the subject.

Clinical Trial Drug Supply
Primary Packaging - Types

- Glass Bottles (amber/clear)
- Polymer Bottles & Closures (e.g. PET, HDPE, etc.)
- Blisters (many different types of materials)
- Tubes, sprays, pumps

Clinical Trial Drug Supply
Primary Packaging – Stability Testing

- Stability Study - List of tests, analytical procedures, criteria, test time points, storage conditions for duration of the study.

- Required when the dosage form is altered (e.g. over encapsulated for blinding purposes) and/or if the packaging has changed from its original, approved container.

- Types of Standard Stability Programs
  - Ambient Conditions (25º C/60%RH) – 12+ Months
  - Intermediate Conditions (30º C/65%RH) – 6+ Months
  - Accelerated Conditions (40º C/75%RH) – 6+ Months

Retest Date (Investigational Product)

- The date assigned by the manufacturer after which the drug substances need to be examined (retested) to ensure that they remain within suitable specifications for use in the manufacture of a drug product

Expiration Dates (Marketed Products)

- Based on body of stability data of the drug in its original closed container.
- It does not mean that drug was unstable after a longer period; it means only that real-time data or extrapolation from accelerated degradation Studies indicate that the drug will still be stable at that date
- Typically 2-3 years
- Once the original container is open the stability of the product can no longer be guaranteed

Clinical Trial Drug Supply
Examples of Analytical Testing

- Disintegration – A physical test that measures the time in which a solid dosage form disintegrates in water.
- Dissolution - A standardized method for measuring the rate of drug release from a dosage form.
- Assay – Measures the percentage of active ingredient in the test product.
- Microbiologic Testing – Test for micro contamination
- Preservative Effectiveness – Tests for effectiveness of preservative system (mostly non-solid dosage forms in multi-use containers)

Clinical Trial Drug Supply
Enrollment Duration

- Duration of enrollment is critical to determining how often study drug will need to be ‘refreshed’ over the course of the study.
- Shelf-life of commercial product is typically 2-3 years and best to plan for 18-24 months of shelf-life remaining at time of initial distribution to sites.
- Studies running longer than 18-24 months will likely require a second manufacturing/packaging campaign of study drug.

Clinical Trial Drug Supply
Enrollment Duration

- **Slower than expected enrollment is the single biggest challenge to managing expiration dating.**
- Often significant pressure for FPI; however, better to wait until as many sites as possible are ready to begin enrolling.

Clinical Trial Drug Supply
SOA/Visit Window Considerations

- Standardize interval of dispensing visits as much as possible.
  - Early visits may dispense just a partial kit
  - For example, 6-month kits with 6 bottles, may dispense 2 bottles at baseline and 4 bottles at a Month 2 visit.
- Maintain a consistent visit window.
  - Recent study was +/- 7 days in Year 1 and then +/- 14 days in Years 2-3
  - One-size kits didn't cover complete visit interval in Years 2-3.
- Always keep visit window in mind when designing kits.
  - For example, 3-month (13 weeks or 91 days) kit with a +/- 5 day visit window will require a 101 days supply.

Clinical Trial Drug Supply
Storage Condition Considerations

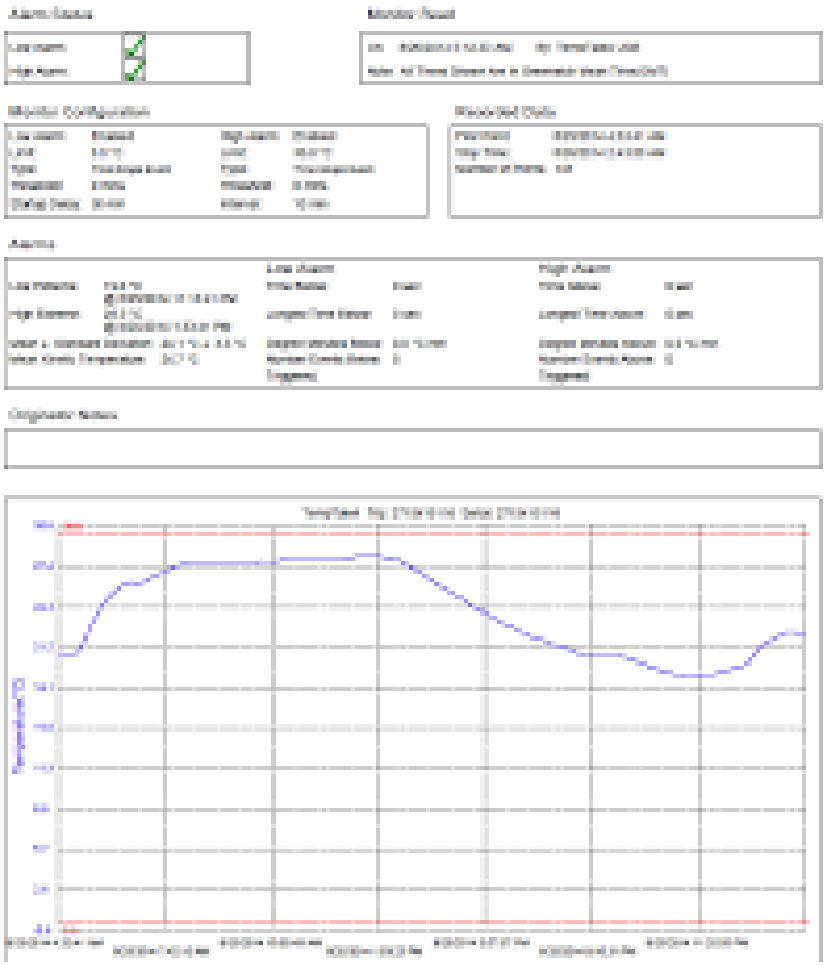
- Frozen
- Refrigerated
- Room Temperature
- Light Sensitive
- Moisture Sensitive
- Transportation
  - Supplies that are temperature sensitive may require special temperature controls and monitoring while in-transit to ensure constant temperature (refrigerated truck, temperature monitoring devices).
- **Most sites have limited storage capabilities (plan initial and restock supplies with site constraints in mind)**

Clinical Trial Drug Supply
In-Transit Temperature Monitoring

TempTale Device

Clinical Trial Drug Supply
In-Transit Temperature Monitoring

TempTale Report



Drug Accountability

- Accountability needs to occur throughout the entire supply chain
- Ensure SOPs in-place at sites to address accountability
- Create appropriate drug dispensing/ accountability logs to be used by sites for drug accountability.

Drug Accountability

DRUG COMPLIANCE/ACCOUNTABILITY LOG

1 0 2 ENROLLMENT ID | SUBJECT ID | INITIALS | SITE NO. | 5 8

Visit #	Kit #	Dispensed By (Initials)	Total # Newly Dispensed #	DATE Dispensed (MM/DD/YEAR)	DATE Returned (MM/DD/YEAR)	Complete Kit Returned (0 = No, 1 = Yes)	# Returned	Comments
SB			Packets 396	/ /	/ /		Packets:	
02			Packets 396	/ /	/ /		Packets:	
03			Packets 396	/ /	/ /		Packets:	
04			Packets 396	/ /	/ /		Packets:	
05			Packets 396	/ /	/ /		Packets:	
T01			Packets 396	/ /	/ /		Packets:	
06			Packets 396	/ /	/ /		Packets:	
T02			Packets 396	/ /	/ /		Packets:	

NOTE: *In the event that site staff or the participant has counted the packets prior to using a kit and notices a discrepancy, please cross off the preprinted number and write in the correct amount.

10/6/06

Clinical Trial Drug Supply
Disposition of Study Drug at Conclusion of Study

- Disposition of materials remaining at site following final accountability:
  - Dispose on site according to institutional policies
    - May encounter local environmental restrictions
  - Return to distributor
  - Send to third-party destruction company (e.g. controlled substances)

- Disposition of materials remaining in central inventory
  - Return to sponsor
  - Send to third party destruction company

Clinical Materials Services Unit (CMSU)

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Rochester, NY 14623
www.clinicalmaterial.com

References

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- Bryom, B. Using IVR in Clinical Trial Management. Applied Clinical Trials. October 2002