

Role of the Investigational Drug Services (IDS) in the Management of Investigational Drugs

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Outline of Presentation

- I. Introduction
- II. Learning Objectives
- III. Review definition of common terms
- IV. Describe the role of IDS in Clinical Research Trials
- V. Discuss the Investigational Drug Management Program (IDMP) and core functions
- VI. Discuss the regulatory framework that governs the operations of the IDS/IDMP and important factors that impact the scope of the IDMP
- VII. Questions & Answers (Q&A) & Closing Remarks
- VIII. References

II. Learning Objectives

At the end of the presentation, participants should:

1. Understand the role of the IDS in the management of investigational drugs
2. Be familiar with the basic components of the Investigational Drug Management Program (IDMP)
3. Understand the regulatory framework that governs the operations of the IDS/IDMP
4. Know the important factors that affect the scope of the IDMP

III. Definitions

- **What is a drug?**
- article recognized in an official compendium source (e.g. United States Pharmacopeia)
- article intended for use in diagnosis, cure, mitigation, treatment, or prevention of disease
- article other than food intended to affect the structure or any function of the body
- article intended for use as a component of any article set forth above

Definition (cont'd)

- What is a Marketed Drug?
 - . drug subject to an FDA approved marketing Application
 - . can be transported or distributed across state lines

Definitions (cont'd)

What is an investigational new drug?

- new drug used in a clinical investigation

What is an investigational drug/agent?

- Any drug used in a clinical research study pursuant to an IRB approved research protocol
 - Marketed drug
 - Investigational New Drug (IND)
 - IND Exempted Marketed Drug

Definitions (cont'd)

- What is an IND?
 - application to the Food and Drug Administration (FDA) to seek permission to test a new drug (or biologic) in human
 - means by which a sponsor technically obtains an exemption from the FDA to transport or distribute a drug across state lines
 - 21 CFR 312

Definitions (cont'd)

Investigator IND

- application submitted by a physician who both initiates and conducts the investigation and under whose immediate direction the investigational drug is administered or dispensed

Emergency (Compassionate) Use IND

- process by which FDA can authorize the immediate shipment of an experimental drug for a use in life-threatening situations in which no standard acceptable treatment is available and there is not sufficient time to obtain IRB approval

Definitions (cont'd)

- Treatment IND
 - experimental drugs showing promise in clinical testing for serious life-threatening conditions
 - made available while the final clinical work is performed and FDA review takes place

IND Exempted Marketed Drug

1. Marketed drug exempted from IND requirements if all of the following apply:
 - Investigation not reported to FDA as a well-controlled study in support of a new indication for use or a significant change in labeling
 - Investigation not intended to support a significant change in the advertising for the drug
 - Investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decrease the acceptability of the risks) associated with the use of the drug

IND Exempted Marketed Drug (Cont'd)

- Investigation is conducted in compliance with the requirements for institutional review (21 CFR 56) and informed consent (21 CFR 50)
- Investigation is conducted in compliance with the requirements of 21 CFR 312.7 (Promotion and sale of investigational drugs)

IND Exemption (cont'd)

2. Exemption for a Clinical Investigation involving a Placebo (21CFR312.2(b)(5))

- clinical investigation involving use of a placebo is exempt if the investigation does not otherwise require submission of an IND

IND Exemption (Cont'd)

3. Exemption for Bioavailability or Bioequivalence Studies (BA/BE) - 21CFR320.31

BA/BE studies using unapproved versions of approved drugs may be conducted without an IND (21CFR320.31), if all of the following conditions are met:

(i) The drug product does not contain a new chemical entity (21CFR314.108), is not radioactively labeled, and is not cytotoxic.

IND Exemption for BA/BE Studies (cont'd)

- (ii) The dose (single dose or total daily dose) does not exceed the dose specified in the labeling of the approved version of the drug product
- (iii) The investigation is conducted in compliance with the requirements for review by an IRB (21CFR56) and the requirements for informed consent (21CFR50)
- (iv) The sponsor meets the requirements for retention of test article samples (21CFR 320.31(d)(1))

IND Exemption (cont'd)

4. Exemption for Radioactive Drugs (21CFR361.1)

- drugs can be used for certain research without an IND when recognized as safe and effective for use in the research. See the 2010 FDA Guidance on Radioactive Drug Research for clarification regarding what research studies may be conducted under the Radioactive Drug Research Committee (RDRC) vs. IND

IND Exemption of Cold Isotopes

Exemption for Studies Using Cold Isotopes of Approved or Unapproved Drugs

In exercising its enforcement discretion, FDA does not intend to object to clinical investigations using cold isotopes of unapproved drugs being conducted without an IND, if the following conditions are met:

(i) The research is intended to obtain basic information regarding the metabolism (including kinetics, distribution, and localization) of a drug labeled with a cold isotope or regarding human physiology, pathophysiology, or biochemistry

IND Exemption of Cold Isotopes (cont'd)

- (ii) The research is not intended for immediate therapeutic, diagnostic, or preventive benefit to the study subject
- (iii) The dose to be administered is known not to cause any clinically detectable pharmacologic effect in humans based on clinical data from published literature or other valid human studies

IV. Role of IDS in Clinical Research Trials

- Supportive
 - Pre-Institutional Review Board (IRB) – consulting and feasibility review
 - IRB – protocol review and approval
 - Post-IRB - drug accountability; record keeping and retention; monitoring; auditing
 - Training and Patient Counseling
 - Miscellaneous
 - Education

Phase 1 Clinical Trials

- Phase 1
 - Examine the agent's pharmacology
 - Define acute effects on normal tissues
 - Determine a safe dose for Phase 2 trials (i.e. evaluate side effects associated with the use of the drug) i.e.. pharmacokinetic
 - possibly gain early evidence on effectiveness of the drug

Phase 2 Clinical Trials

- Determines whether an agent has pharmacologic activity (e.g. antitumor activity) against a particular disease
- Estimates response rate in a defined patient population
- Disease-oriented: Phase 2 measures disease parameters
- Controlled studies

Phase 3 Clinical Trials

- Phase 3 trials
 - expanded studies performed after preliminary evidence suggesting effectiveness
 - intended to gather additional information about effectiveness and safety in order to properly evaluate the overall benefit-risk relationship of the drug
 - Compares efficacy of experimental therapy with that of a standard or control therapy if significant activity is observed in any disease during Phase 2

Role of IDS in the Management of the Investigational Drug Program (IDMP)

- A Delegated authority of the Principal Investigator (PI)
 - PI must retain oversight responsibilities
 - 21 CFR 312.60 - 312.61; 21 CFR 312.52

Essential Components of the Investigational Management Program (IDMP)

- Written policies and standard operating procedures
- Data Management system(s)/HIPAA Compliant
 - Recordkeeping
 - Protocol Management (including amendments)
 - Investigator Brochures (IB)
 - Drug inventory

Essential components of the IDMP (cont'd)

- Resources
 - Personnel
 - Office Space and Equipment
 - Storage
 - Sterile drug preparation area (USP 797)

IDMP: Core Functions of IDMP

- Drug Procurement (Starter supplies; patient specific supplies)
 - Drug Requests
 - Drug Receipts/Invoices
 - Inventory Control
- Prescription processing
 - Prescription review/entry
 - Filling/preparation of prescription (e.g. drug blinding)

- Dispensing
 - Labeling
 - Recording/documentation of dispensing
 - Prospective Drug Review Evaluation
 - Counseling
 - Billing

IDMP: Core Functions of the IDMP (cont'd)

- Patient drug returns
- Drug returns to sponsor or designee (e.g. unused)
- On-site disposal/destruction of drugs
- Quality Assurance

VI. Regulatory Framework Governing operations of IDS Operations

Federal laws and regulations (Title 21)

- . IND
- . Informed Consent
- . Good Clinical Practice (GCP)

- Drug Enforcement Agency (DEA)
 - . Controlled substances
 - . Special registration requirements

IDMP (cont'd)

.Local laws and regulations

- prescriptive authority
- dispensing authority
- drug distributor registration
- Prospective Drug Regimen Reviews

IDMP Cont'd

- Institutional policies and procedures (risk/benefit assessment)
 - IRB
 - Pharmacy
 - IDS
 - Scope of Practice/Responsibilities of study team members

IDMP (Cont'd)

Sponsor

- study design (randomized/blinded/placebo)
- Multicenter – Central Drug Distribution (monitor/audit)
- International
- Documentation –electronic; interactive voice recognition (IVRS)/interactive web recognition system (IWRS)
- Drug supplies (National Cancer Institute vs. Industry-Sponsor)
- Drug returns/destruction

IDMP (Cont'd)

Principal Investigator

- .scope of delegated duties/responsibilities (drug storage in office vs. IDS)
- .oversight

IDMP (cont'd)

- PATIENT STATUS

- .Inpatient - counseling

- .Outpatient –counseling; drug shipment

- .Out-of-State Patient – drug shipment

IDMP (Cont'd)

Regulatory framework that governs the operations of the IDS and its impact on the IDMP

- .Federal laws and regulations (21 CFR 312; FDA; DEA)
 - status of the test article (IND; IND-Exempt; Marketed product; other e.g. cold isotopes)
- .Local laws and regulations
- .Institutional policies and procedures (risk/benefit assessment)
- .Protocol and Investigator Brochure (IB)
- .Patient – informed consent

Quality Assurance Program

- Quality Assurance
- Data accuracy - documentation must accurately reflect the primary source documentation
- Protocol compliance –
- Procedural Requirements – approval documents must be kept on file

District of Columbia Municipal Regulation (Title 22 Section 1912)

- A container in which a prescription drug or device is sold or dispensed must bear a label containing the following information:
 - Name, address, and telephone number of pharmacy
 - Name of patient
 - Name of prescribing practitioner
 - Date of filing

District of Columbia Municipal Regulation (Title 22 Section 1912) – cont'd

- drug name i.e. generic, chemical, or brand name of the drug unless omission is specifically requested by the prescriber in writing pursuant to the District of Columbia Prescription Drug Price Information Act
- Strength, dosage, and quantity of the drug dispensed
- Directions for use and cautionary statements, if any, contained in the prescription or required by law

District of Columbia Municipal Regulation (Title 22 Section 1912) – cont'd

- Serial number of the prescription or prescription number
- Expiration date of the product according to the manufacture or one (1) year from the date the drug or medical device is dispensed, whichever comes first, subject to the discretion of the pharmacist to select an earlier date on which the life of a compounded drug product may expire
- Controlled substance label shall include a clear, concise warning that it is a crime to transfer the drug to any person other than the patient

District of Columbia Municipal Law

- Recordkeeping
- Must maintain current, complete, and accurate record of all prescription drugs and devices received, sold, compounded, dispensed, or otherwise disposed of by pharmacy for a period of five (5) years

District of Columbia Municipal Regulations

- Patient Counseling of inpatient facility:
 - pharmacist or a licensed health care professional authorized to administer drugs (Title 22, Section 1916.7)
 - Following review of a patient's medical record and prior to dispensing a drug or medical device, a pharmacist (RPh) shall make a verbal offer to counsel (Title 22, Section 1919)
 - First time prescription (Rx) dispensed to patient
 - Rx not previously dispensed to patient in same dosage form, strength, or written directions
 - Once yearly on maintenance medications
 - Whenever RPH deems it warranted in the exercise of professional judgment

District of Columbia Municipal Regulations

- Prospective Drug Regimen Review
- A pharmacist shall, prior to or at the time of dispensing a prescription drug order, review the patient's medication record and each prescription drug order presented for dispensing (Title 22, Section 1918)

District of Columbia Municipal Regulations

- Prescription Drug
 - drug which under federal law is required to be labeled with a cautionary statement prior to being dispensed or delivered “Caution: Federal law prohibits dispensing without a prescription” or “Caution: Federal law restricts this drug to use by, or on the order of, a licensed veterinarian
 - drug restricted to use by health professionals and allied practitioners for research District of Columbia Municipal Regulation (Title 22 Section 1912)

District of Columbia

Health Professionals with Dispensing authority

- .Medical Doctors
- .Physician Assistant (delegation agreement with supervising physician)
- .Advanced Registered Nurse Practitioner (ARNP) only
- Pharmacists

VII. CONCLUSION

- Question & Answers

- Closing Remarks

VIII. References

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2. <http://www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/InvestigationalNewDrugINDorDeviceExemptionIDEProcess/default.htm>
3. FDA Guidance for Industry Investigational New Drug Applications (INDs)—Determining Whether Human Research Studies Can Be Conducted Without an IND – October 2010

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6. District of Columbia Official Code: Title 48

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7. Understanding FDA Regulatory Requirements for Investigational New Drug Applications for Sponsor-Investigators. ME Holbein. Journal of investigative Medicine, August 2009, vol. 57(6): 689-695
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9. National Association of Boards of Pharmacy (NABP)
2011 Survey of Pharmacy Law – Dispensing Authority