DAIDS
Bethesda, MD USA

POLICY

Determination of Investigational New Drug Application (IND)

Approval Date: 20 DEC 06 No.: DWD-POL-RA-001.02
Effective Date: 05 FEB 07

NOTE: THIS DOCUMENT HAS BEEN REPLACED BY THE FEBRUARY 27, 2009 POLICY ENTITLED, "DETERMINATION OF INVESTIGATIONAL NEW DRUG APPLICATION (IND)" VERSION 3.0.

1.0 PURPOSE

The purpose of this policy is to provide guidance in determining whether or not an Investigational New Drug Application (IND) needs to be filed with the U.S. Food and Drug Administration (FDA).

2.0 SCOPE

This policy applies to all trials funded and/or sponsored by the Division of Acquired Immunodeficiency Syndrome (DAIDS). This may include clinical trials evaluating drugs and/or biological products that are approved to be lawfully marketed in the United States and are being considered for an investigational use.

3.0 BACKGROUND

DAIDS collaborates with industry, academia, the international scientific community and the communities of persons most affected by HIV/AIDS to develop and test drugs and biological products to prevent and manage HIV infection. DAIDS complies with all applicable U.S. regulations governing the evaluation of investigational drugs and/or biological products. The IND is the formal submission made to the FDA that indicates a sponsor's intention to conduct a clinical trial with an investigational drug or biological product. It is the means through which the sponsor technically obtains the authorization to conduct clinical trials according to the protocols submitted to the FDA in the IND application.

4.0 DEFINITIONS

Biological product: Any virus, therapeutic serum, toxin, antitoxin, or analogous product available to prevent, treat or cure diseases or injuries in man. The terms "biological product" or "biologic" are deemed to be synonymous for purposes of this policy.

Clinical investigation: Any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects.

Code of Federal Regulation (CFR): The regulatory and legal guide for the preparation of INDs to be submitted to either the Center for Biologics Evaluation

and Research (CBER) or the Center for Drug Evaluation and Research (CDER) at the FDA.

Drug: Article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals.

IND: An investigational new drug application submitted to the FDA.

Investigational new drug: A new drug or biological product that is used in a clinical investigation. The terms "investigational new drug" and "investigational drug" are deemed to be synonymous for purposes of this policy.

Legally marketed product: A product that received licensure or approval for marketing in the United States (U.S.).

Office for Policy in Clinical Research Operations (OPCRO): An office in the Division of AIDS (DAIDS) that provides a variety of clinical trials management resources and oversight to DAIDS clinical research portfolio. This includes overseeing the development, standardization, implementation and execution of policies, procedures and standards of conduct for all of DAIDS domestic and international clinical research.

Principal Investigator (PI): A qualified person designated by the applicant institution to direct the research. PIs oversee the scientific and technical aspects of a grant and the day-to-day management of the research.

Regulatory Affairs Branch (RAB): A branch in the Office for Policy in Clinical Research Operations (OPCRO) in the Division of AIDS (DAIDS), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH). RAB performs regulatory surveillance over all clinical trials funded and/or sponsored by DAIDS.

Sponsor: An individual or pharmaceutical company, government agency, academic institution or other organization who takes responsibility for and initiates a clinical investigation. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator.

Sponsor-Investigator: An individual who submits an IND to the FDA and initiates, conducts, alone or with others, a clinical investigation at a trial site and under whose immediate direction the test article is administered or dispensed to a subject.

Subject: A human who participates in an investigation, either as a recipient of the investigational new drug or as a control. A subject may be a healthy human or a patient with a disease.

Tentative Drug Approval: If a generic drug product is ready for approval before the expiration of any patents or exclusivities accorded to the reference list drug product (an approved drug product to which new generic versions are compared), FDA issues a tentative approval letter to the applicant. The tentative approval letter details the circumstances associated with the tentative approval. FDA delays final approval of the generic drug product until all patent or exclusivity issues have been resolved. A tentative approval does not allow the applicant to market the generic drug product in the United States.

U. S. Food and Drug Administration (FDA): A public health agency within the United States Department of Health and Human Services. FDA's mission is to promote and protect public health by helping safe and effective products reach the market in a timely way and monitoring of products for continued safety after they are in use as authorized by The Federal Food and Cosmetic Act. The Agency regulates all clinical investigations in support of marketing applications.

For additional definitions see DAIDS glossary.

5.0 RESPONSIBILITES

RAB is responsible for determining if a clinical trial needs to be conducted under an IND in accordance with the applicable U.S. regulations. This decision may require RAB's consultation with the FDA, pharmaceutical companies, protocol team and/or PI and other DAIDS program staff. RAB is also responsible for maintaining all IND documentation in a secure location.

The *Principal Investigator* (PI) is responsible for submitting all the necessary documents to the host country regulatory authorities for studies conducted outside of the United States. Documentation of all correspondence and approval from the host country regulatory authorities must be provided to the appropriate DAIDS program staff prior to study initiation in the host country.

6.0 POLICY

6.1 IND Sponsor - DAIDS reserves the right to serve as the IND Sponsor of any clinical trial that it funds. In some circumstances, DAIDS may agree, in advance and through a Clinical Trial Agreement (CTA) that a pharmaceutical

company collaborator serves as the Sponsor. On a select, case-by-case basis, DAIDS may agree that an investigator serve as the Sponsor (Sponsor-Investigator). The specific requirements of the Sponsor-Investigator will be agreed to in advance and be included in the contract Statement of Work or the Grant Terms of Award (notice of Grant Award). DAIDS reserves the right to submit an IND to the FDA even if there is no plan to conduct the study in the U.S and as such must follow the U.S. Code of Federal Regulations.

6.2 Investigational New Drug or Biologic Product - If an investigational new drug or biologic has not received marketing or tentative drug approval from the FDA, then the sponsor must submit an IND pursuant to 21 CFR 312 to the FDA. The clinical trials are allowed to begin 30 calendar days after the FDA receives the IND, unless the sponsor is notified by the FDA that the investigations described in the IND are subject to a clinical hold.

Tentative drug approval by the FDA is a key regulatory mechanism to support the availability of drugs for the President's Emergency Plan for AIDS Relief (PEPFAR). Tentative approval, whether for a new drug application or a generic drug application, can provide low-cost versions of innovator drugs to the developed world for purchase under the emergency plan. The tentative approval means that existing patents and exclusivity prevent the product from being sold in the United States.

6.3 Lawfully Marketed Drug and Biologic Products - If a drug or biologic product is already lawfully marketed in the U.S., the IND regulations state that clinical investigation of a drug or biologic product is exempt from the requirements for an IND if **all** of the following apply:

6.3.1 The investigation is not intended to be reported to the FDA as a well-controlled study in support of a new indication for use, nor intended to be used to support any other significant change in the labeling for the drug or biologic product.

6.3.2 The investigation is not intended to support a significant change in the advertising for a prescription drug or biologic product.

6.3.3 The investigation does not involve a change in route of administration, dosage level, or patient population, or other factor that significantly increases the risks (or decreases the acceptability of risks) associated with use of the drug or biologic product.

6.3.4 The investigation is conducted in compliance with the requirements for institutional review and informed consent regulations.

6.3.5 The drug or biologic product may not be represented as safe or effective for the purposes for which it is under investigation, nor may it be commercially distributed or sold.

6.4 Generic Products

6.4.1 If the generic product has received approval in the host country or from the World Health Organization (WHO) but has not received approval for marketing or tentative drug approval from the FDA, then the Sponsor must submit an IND. If the Protocol Team elects to use an unapproved generic formulation of a study drug after finalization of the protocol, the team must inform RAB because a determination for a new IND or consultation with the FDA may be needed.

6.5 FDA Consultation

6.5.1 If there is any question regarding the need to submit an IND to the FDA, RAB will consult with the FDA after conferring with pharmaceutical companies, the protocol team and/or PI and other DAIDS program staff.

7.0 REFERENCES

Code of Federal Regulations, Title 21, Part 312
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm

Center for Biologics Evaluation and Research
www.fda.gov/cber/

Center for Drug Evaluation and Research
www.fda.gov/cder/

8.0 INQUIRIES

Questions and comments regarding this policy may be directed to the OPCRO Policy Group at: NIAIDOPCROPOLICYGROUP@mail.nih.gov

9.0 AVAILABILITY

This policy is available electronically at the following URL:
http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/Default.htm

The signed original is maintained in the OPCRO policy office.

10.0 CHANGE SUMMARY

This policy replaces Version 1.0 dated 14 Jul 06.

11.0 APPENDICES

None

12.0 APPROVAL

/Richard Hafner, MD/
Richard Hafner