DAIDS
Bethesda, MD USA

POLICY

Use of Drug Products Not Marketed in the United States

Approval Date: 21 JAN 2015 No.: DWD-POL-RA-014.02
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CHANGE SUMMARY NOTE: This policy has been reviewed for accuracy and updated to meet 508 compliance guidelines. All definitions have been removed and replaced with a link to the DAIDS glossary. This version supersedes version 1.0 dated 24 JUN 2011.

1.0 PURPOSE

The purpose of this policy is to describe the process for authorizing the use of study products in NIAID (DAIDS)-supported and/or -sponsored clinical trials, when such products have not been approved or tentatively approved by the U.S. FDA, but are marketed elsewhere. This policy is intended to address situations where a protocol specifies a product but not the manufacturer, and the product is not being supplied by the trial itself.

2.0 SCOPE

This policy applies to both network and non-network NIAID (DAIDS) - supported and/or -sponsored clinical trials conducted outside of the United States that use non- United States Food and Drug Administration (FDA) approved or tentatively approved products. Non-FDA "approved products" refers to products marketed outside of the U.S. that have not received FDA approval or tentative approval.

For the purposes of this policy, the term "study product" refers to any prescription or over-the counter drug, biologic, vaccine, or device that is identified in the protocol as a study required product. The term is not intended to include concomitant medications, medications specified in the protocol for the treatment of adverse events, or products that are not approved for use in any country.

3.0 BACKGROUND

NIAID (DAIDS)-supported and/or -sponsored clinical trials frequently obtain study products by donation. The availability of such donations can have a significant impact on the ability to enroll participants, especially in resource-constrained settings. As not all study products are donated from pharmaceutical companies, sites must often rely on locally supplied products. In fact, at many DAIDS-supported trial sites located outside of the United States, non-FDA approved products may be the only available option.

However, the use of non-FDA approved study products in clinical trials poses potential scientific and regulatory challenges. For example, the products may not have undergone the rigorous study and regulatory scrutiny required to

adequately establish safety, effectiveness, and product manufacturing quality. Therefore, the purpose of this policy is to define acceptable standards for the use of non-FDA approved products in NIAID (DAIDS)-supported and/or -sponsored clinical trials.

This policy provides criteria for determining the acceptability of marketed drugs in non-U.S. countries that have not received FDA approval or tentative approval. The procedures in this policy are intended to ensure that the use of non-FDA approved drugs and biological products will not compromise the safety of participants, scientific validity, or integrity of trials.

4.0 DEFINITIONS

For definitions, see DAIDS glossary.

5.0 RESPONSIBILITIES

The responsibilities listed in this section will not be applicable in every case. For instance, Network-related responsibilities do not apply when a product is being provided in a non-Network trial.

Clinical Research Site Leader

The *Clinical Research Site Leader* within a Network will:

1. Make the initial determination of the need to request the use of a non-FDA approved product that does not otherwise qualify based on the criteria in this document, including preliminary determination of whether or not such use will unacceptably impact participant safety or the scientific integrity of the protocol;

2. Obtain approval by the Protocol Chair;

3. Submit a request to use the product to the Network Leadership;

4. Ensure that products used at their site throughout the course of the study meet the criteria specified in Section 6.0 of this policy.

Network Leadership

The *Network Leadership* will:

1. Inform the DAIDS Program Director, DAIDS Medical Officer, and DAIDS Program Officer about requests from sites to use a non-FDA approved product;

2. Set up a Review Committee comprised of independent experts to review the available information on the drug;

3. Advise the Network Leadership regarding any potential impact on the scientific integrity of the trial or study participant safety;

4. Make a recommendation on the appropriateness of using the non- FDA approved product to the DAIDS Program Director.

Principal Investigator

The *Principal Investigator* of a non-Network trial will provide the rationale for use of the non-FDA approved product to the DAIDS Program Officer, and documentation that use of the product will not unacceptably impact participant safety or the scientific integrity of the protocol. This information will be reviewed by an ad hoc committee created by the DAIDS Program Director.

Protocol Team

The *Protocol Team* will ensure that the case report forms require documentation of the use of non-FDA approved products during the trial. The team will also consider whether an analysis by site, country, or study product is warranted. This may require discussion with either the study monitoring committee or data safety monitoring committee if there is a need to monitor these data while the study is ongoing.

DAIDS Program Director

The *DAIDS Program Director,* or designee, will:

1. Review the information supplied to the program;

2. If needed, convene an ad hoc committee to review information submitted by a non-Network PI;

3. Make a final determination regarding whether use of the non-FDA approved product is justified (i.e., unlikely to interfere with the scientific integrity of the clinical trial or pose an unacceptable risk to participant safety);

4. Will communicate all determinations to the site staff, Protocol Chair, and DAIDS staff, including the Program Officer, Medical Officer, Pharmaceutical Affairs Branch, and appropriate OPCRO staff.

6.0 POLICY

6.1 Criteria For Accepting the Use of Non-FDA Approved Products in NIAID (DAIDS)-Supported and/or -Sponsored Clinical Trials

6.1.1 In order for a non-FDA approved product to be considered acceptable under this subsection, the product must be approved for marketing in the country where the trial is being conducted. Such evidence may include information from an official website of the country's medicines regulatory authority (MRA) or ministry of health (MoH) or other official government publication. The product must also meet at least one of the following additional criteria:

a) Sourced from, manufactured and approved for marketing in a country listed under Title 21 U.S.C. 382 (b)(1)(A).

Note: These countries are Australia, Canada, Israel, Japan, New Zealand, Switzerland, South Africa, and members of the European Union or a country in the European Economic Area (all European Union member states (plus Iceland, Lichtenstein, and Norway) and the European Free Trade Association).

b) Manufactured and approved for marketing in a member country of the Pharmaceutical Inspection Co-operation Scheme (PIC/S).

Note: PIC/S uses the "Good Manufacturing Practice Guideline for Active

Pharmaceutical Ingredients" (ICH Q7A) developed by the International Conference on Harmonisation.

c) Prequalified under the World Health Organization (WHO) Pre-Qualification Programme Note: The WHO maintains a list of products that meet published WHO manufacturing standards. A current list of such products can be obtained here.

d) Approved under Article 58 of Regulation (EC) Number 726/2004 by the European Medicines Agency (EMA) for medicinal products for human use intended exclusively for markets outside of the European Union (EU).

Note: Medicines eligible for this procedure are used to prevent or treat diseases of major public health interest, including medicines for WHO target diseases such as HIV/AIDS, malaria, and tuberculosis. Refer to the European public assessment report (EPAR) publications or directly to the manufacturer of the drug products to determine whether a product has been reviewed by the EMA under Article 58.

e) Obtained through the Green Light Committee (GLC) Initiative/ Global Drug Facility (GDF)

Note: The GLC Initiative/GDF provides access to second- line anti-tuberculosis drugs for the treatment of multi-drug resistant tuberculosis, utilizing WHO standards including the WHO Prequalification Programme.

f) Approved by the Agência Nacional de Vigilância Sanitária (ANVISA) Note: ANVISA is the Brazilian National Health Surveillance Agency, and uses Good Manufacturing Practices (GMP) regulations based on WHO standards.

g) Approved by the Kingdom of Thailand Food and Drug Administration

Note: The GMP regulations of this agency are based on WHO standards. Revisions are currently underway to conform to GMP standards established by PIC/S, which will also meet the criteria for use in a NIAID (DAIDS)-

supported and/or -sponsored clinical trial.

h) Approved by the State Food and Drug Administration (SFDA) of the People's Republic of China

Note: The SFDA regulates pharmaceutical manufacturing in accordance with the Drug Administration Law of the People's Republic of China and Regulations for Implementation of the Drug Administration Law of the People's Republic of China. The GMP regulations of the SFDA are comparable to the US FDA GMP regulations located in 21 CFR Part 211.

i) Obtained through The Global Fund

Note: Products obtained through The Global Fund are authorized for use by the regulatory authority in the country where they will be used, and must either be prequalified under the WHO Prequalification Programme, authorized for use by a stringent regulatory authority as defined by The Global Fund guidance, or recommended for use by The Global Fund Expert Review Panel, a group hosted by the WHO.

6.1.2 For non-FDA approved products that do not meet the criteria in Section 6.1.1, the site must provide all of the following information in support of its request for use if available:

a) Evidence that the MRA or MoH in the country where the clinical trial is conducted has considered in its review of the marketing application dossier compliance with globally accepted current good manufacturing practices (GMP) and bioequivalence data.

b) Safety and efficacy information collected in the country where the product is used.

c) A summary provided by the Principal Investigator (PI) or Site Leader that includes relevant peer- reviewed scientific literature and collated clinical experience data regarding the safety and efficacy of the product. If neither published data nor collated data exists, the PI must provide

documentation of convincing direct knowledge of patient experience with the product.

6.2 Process For Accepting the Use of Non-FDA Approved Products in NIAID(DAIDS)-Supported and/or Sponsored Clinical Trials

6.2.1 The CRS Leader shall provide the information specified in Section 6.1.2 to the Network Protocol Chair.

6.2.2 The Network Protocol Chair shall submit in writing the rationale for use of a non-FDA approved product to the appropriate Network Leaders, including the source of the product (e.g., manufacturer and distributor names, and dosage size), and request evaluation by the Network Leaders.

6.2.3 The Network Leaders will evaluate the request, and provide their recommendation regarding approval to the DAIDS Program Director, along with any necessary supporting documentation.

6.2.4 For non-Network trials, Principal Investigators shall submit the information described in Section 6.1.2 to the DAIDS Program Officer. This information will be reviewed by an ad hoc committee created by the DAIDS Program Director, and a copy of the committee's recommendation will be sent to the Principal Investigator and the Program Director.

6.2.5 The recommendation to the DAIDS Program Director can occur at any time during a trial, but Site Leaders, Protocol Chairs, Network Leadership, and non-Network Principal Investigators are encouraged to accomplish this as early as possible so that appropriate study product choices are available to participants (i.e., prior to study initiation).

6.2.6 The DAIDS Program Director, or designee, will review the recommendations and information provided, and make a final determination regarding the proposed use of the non-FDA approved product. The Program Director will communicate all determinations to the site staff, Protocol Chair, and DAIDS staff, including the Program Officer, Medical Officer, Pharmaceutical Affairs Branch, and

appropriate OPCRO staff.

6.2.7 Site activation for a trial or continued site participation is contingent on a determination that use of a non-FDA approved product will not impact participant safety or the scientific integrity of the trial.

7.0 REFERENCES

Guidance for Industry: Exports Under the FDA Export Reform and Enhancement Act of 1996 Part VII. Exports of Unapproved Drugs, Biological Products, and Devices

Guidance for Industry, ICH Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients

Pharmaceutical Inspection Co-operation Scheme (PIC/S)

World Health Organization (WHO) Pre-Qualification Programme

Stop TB Partnership, Global Drug Facility

8.0 INQUIRIES

Questions and comments regarding this policy may be directed to the OPCRO Policy Group

9.0 AVAILABILITY

This policy is available electronically on the Division of AIDS (DAIDS) Clinical Research Policies and Standard Procedures webpage.

10.0 APPENDICES

None

11.0 APPROVAL

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