- Report any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction to the FDA and to all investigators (as applicable) no later than 15 calendar days after determining that the information qualifies for reporting .
- When the treating physician has completed treatment of the patient with the drug/biologic or if it has been decided not to treat the patient, the FDA must be notified so that the IND may be withdrawn. The final report to the FDA should include a summary of the results of treatment, including adverse effects, and information concerning the disposition of any unused supplies of the test article.

b. If no prior expanded access IND was obtained (only verbal FDA approval), the following reporting actions are required:

- Submit an expanded access IND application **within 15 working days** of FDA's initial authorization of the expanded access use (21 CFR 312.310(d)(2)).

## 8.4 EXPANDED ACCESS USE OF INVESTIGATIONAL DRUGS/BIOLOGICS

Expanded access refers to the use of an investigational drug/biologic when the primary purpose is to diagnose, monitor, or treat a patient rather than to obtain the kind of information about the drug/biologic (i.e., safety and efficacy data) that is generally derived from clinical trials. Expanded access to an investigational drug/biologic can only be provided under an expanded access IND or protocol if the sponsor is actively pursuing marketing approval of the drug/biologic for the expanded access use.

Expanded access, access, and treatment use may also refer to (1) use in situations when a drug/biologic has been withdrawn for safety reasons, but there exists a patient population for whom the benefits of the withdrawn drug continue to outweigh the risks; (2) use of a similar, but unapproved drug/biologic (e.g., foreign-approved product) to provide treatment during a shortage of the approved drug/biologic; (3) use of an approved drug/biologic where availability is limited by a risk evaluation and mitigation strategy (REMS) for diagnostic, monitoring, or treatment purposes, by patients who cannot obtain the drug/biologic under the REMS; or (4) use for other reasons.

There are three categories of expanded access to an investigational drug/biologic:

- Expanded access for individual patients, including for emergency use.
- Expanded access for intermediate-size patient populations (generally smaller than those typical of a treatment IND or treatment protocol — a treatment protocol is submitted as a protocol to an existing IND by the sponsor)
- Expanded access for widespread treatment use through a treatment IND or treatment protocol (designed for use in larger patient populations)

For each category of expanded access, there are two types of regulatory submissions that can be made:

1. Expanded access ***protocol*** submitted as a protocol amendment to an existing IND (i.e., an expanded access protocol). An expanded access protocol submission for expanded access should be used only if the sponsor has an existing IND — typically under which

the sponsor is developing the drug/biologic for marketing. When there is an existing IND in effect, the FDA encourages the submission of an expanded access protocol, rather than a new expanded access IND; having all expanded access and clinical trial use consolidated under a single IND may facilitate identification of safety concerns, may make the administrative process less burdensome for sponsors and FDA, and may help in product review.

2. ***New*** expanded access IND submission, which is separate and distinct from any existing INDs and is intended only to make an investigational drug/biologic available for treatment. A new expanded access IND submission generally should be used when (1) there is no existing IND in effect for the drug/biologic or, more commonly, (2) when the sponsor of an existing IND declines to be the sponsor of the expanded access use (e.g., for an individual patient use, the sponsor of the existing IND may prefer that a patient's physician take on the role of sponsor-investigator and submit a separate individual patient IND).

When proposing an expanded access application for treatment of groups (or populations) of patients, an applicant should ensure that their proposal satisfy all of the following criteria:

1. Patient(s) have a serious or immediately life-threatening disease **or** condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition;
2. The potential patient benefit justifies the potential risks of the treatment and the potential risks are not unreasonable in the context of the disease or condition to be treated; and
3. The expanded use of the investigational drug for the requested treatment will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the product.

The party who (1) submits a request to open an expanded access application and (2) receives FDA's authorization to use the investigational product is considered the sponsor of the application. In the absence of any other sponsor (e.g. pharmaceutical company), the treating physician is the sponsor of the expanded access.

Sponsors of expanded access applications have the same Investigators' Responsibilities as sponsors of IND applications intended for clinical investigations. The procedures for safety, annual, and other IND Application Reporting for expanded access applications are like those for investigational IND applications. The requirements for mandatory IND Application Safety Reporting are the same as for all other IND applications.

Submission of an expanded access application for a group of patients would be appropriate in any of the following situations:

i. The intended investigational drug/biologic is not being developed, for example, because the disease or condition is so rare that the sponsor is unable to recruit patients for a clinical trial.

ii. The intended investigational drug/biologic is being developed and studied in a clinical trial, but patients requesting the expanded access use are unable to participate in the trial. For example, patients may not be able to participate in the trial because they have a different disease or stage of disease than the one being studied or otherwise do not

meet the enrollment criteria, because enrollment in the trial is closed, or because the trial site is not geographically accessible.

iii. The intended investigational drug/biologic is an approved drug product that is no longer marketed for safety reasons or is unavailable through marketing due to failure to meet the conditions of the approved application.

iv. The intended investigational drug contains the same active moiety as an approved drug product that is unavailable through marketing due to failure to meet the conditions of the approved application or a drug shortage.

When the expanded access IND or protocol has been procured from the FDA the following must be submitted to the IRB:

a. Initial Application in Cayuse IRB: an outline of the rationale for the use, including a description of available therapeutic options, an explanation of why use of this test article is preferable, description of the disease, the method of administration of the drug, dose, and duration of therapy. A description of the clinical procedures, laboratory tests, or other monitoring necessary to evaluate the effects of the drug and minimize its risks

b. A copy of the written consent form that will be used to obtained informed consent. The consent form must contain all the elements of consent per FDA regulations, and must explain the purpose of the use of this investigational drug. The consent document must include an explanation of what data will be collected regarding the administration, to whom it will be shared and for what purpose(s), and the reporting requirements to the FDA and/or sponsor. Investigators treating a patient(s) with an investigational drug under expanded access are responsible for ensuring that the informed consent requirements are met.

c. The Approval/Acknowledgment IND or protocol letter from the FDA.

d. A copy of the current Investigational Brochure for the investigational drug.

Individual expanded access INDs, including emergency use, may be reviewed by the IRB Chair or other designated IRB member for concurrence before treatment use begins, if authorization for the waiver of convened IRB review has been obtained from the FDA (via FDA Form 3926). This is only applicable for protocols intended to treat one patient. Expanded access INDs for intermediate-size patient populations or widespread treatment use through a treatment IND or treatment protocol will be reviewed at a convened IRB meeting, following standard IRB procedures.

## 8.5 GROUP C TREATMENT IND

The Group C Treatment IND was established to provide a means for the distribution of investigational agents to oncologists for the treatment of cancer under protocols outside the controlled clinical trial. Group C drugs are generally drugs that have completed Phase III trials and have shown evidence of reproducible efficacy in a specific tumor type. They are distributed only by the NIH under NCI protocols.

Although treatment is the primary objective in these cases, efficacy and safety data are also collected. However, since administration of Group C drugs is not done with research intent, the FDA usually grants a waiver of IRB requirements (21 CFR 105). If an investigator plans to treat cancer patients with Group C drugs, he or she is required to submit a copy to the IRB of the following documentation: (a) FDA letter waiving the requirement for IRB review, (b) the treatment