

APPENDIX C

"OFF-LABEL" AND INVESTIGATIONAL USE OF APPROVED DRUGS AND BIOLOGICS

A. "Off-Label" Use of Approved Drugs and Biologics for Patient Management

Good medical practice and patient interests require that physicians be able to use approved (i.e., marketed) drugs and biologics according to their best knowledge and judgement. If a physician uses for patient management, an approved product for an indication that does not appear in its approved labeling, s/he has the responsibility to be well informed about the product, to base such "off-label" use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects.

The "off-label" use (including the emergency "off-label use") of an approved drug or biologic for treatment or diagnostic purposes (i.e., patient management) in the manner described above is considered part of the "practice of medicine" and does not require the submission of an investigational new drug (IND) application or review and approval by the IRB.

B. "Off-Label" Use of Approved Drugs and Biologics in the Context of Research

At a minimum,¹ a research protocol and informed consent document should be developed for IRB review and approval if the intended use of the approved drug or biologic involves research; i.e., a) a systematic investigation to evaluate the safety and effectiveness of the drug; b) the collection of data with the intent to report such in a scientific publication; c) any consideration other than the direct welfare of the patient (e.g., a selection between the drug or placebo, or between two or more equivalent drugs, based on randomization; the administration of the drug to a normal "control" subject); or d) a use not based on firm scientific rationale and/or medical evidence.

According to FDA regulations, the "research use" of an approved drug or biologic does not require the submission of an IND if:

- 1) it is not intended to be reported to the FDA in support of a new indication for use or to support any other significant change in the labeling of the product;

¹Although it may not be required, the FDA encourages the submission of investigational new drug applications that address studies of the safety and effectiveness of approved drugs and biologics for "off-label" uses.

- 2) it is not intended to support a significant change in the advertising for the product;
- 3) it does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of risks) associated with the use of the product; and
- 4) it is conducted in compliance with the requirements for IRB review and informed consent.